DESIGN AND EVALUATION OF GASTRO RETENTIVE FLOATING DRUG DELIVERY SYSTEM OF VALSARTAN

Dissertation submitted to

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CERTIFICATE

This is to certify that the dissertation entitled **"DESIGN AND EVALUATION OF GASTRO RETENTIVE FLOATING DRUG DELIVERY SYSTEM OF VALSARTAN"** submitted by **Miss. B. YUGANYA** in partial fulfillment of the requirement for the Degree of **Master of Pharmacy** in **Pharmaceutics** is a bonafide work carried out by her, under the guidance and supervision of **Prof. Mr. A. Abdul Hasan Sathali, M.Pharm., (Ph.D).,** Professor and Head, in the Department of Pharmaceutics, Madurai Medical College, Madurai-20, during the academic year 2011 – 2012. This dissertation is forwarded to the Controller of Examination, The Tamilnadu Dr. M.G.R. Medical University, Chennai.

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I wish her success in all his endeavors.

Place: Madurai **(Prof. Mr. A. Abdul Hasan Sathali)**

Date:

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"Lives of great men all remind us
We can make our lives sublime
And departing leave behind us
Foot prints on the sands of time"

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CONTENTS

CHAPTER – I

INTRODUCTION

For decades an acute condition or chronic illness is being clinically treated through delivery of drugs to the patients in form of some pharmaceutical dosage forms like tablets, capsules, creams, liquids, ointments, aerosols, etc.

To attain and maintain the concentration of an administered drug within therapeutically effective range, it is often required to take drug dosage several times and this result in a fluctuating drug level in plasma. Controlled or sustained drug delivery systems have been introduce to overwhelm the problem of fluctuating drug levels related with conventional dosage forms (Vyas.S.P & Khar, 2002) , as shown in Figure 1 **(**Jaiswal.S.B *et al*., 2007).

Fundamentally, there are three modes of drug delivery which are,

- **SUSTAINED RELEASE DRUG DELIVERY SYSTEM**
- **CONTROLLED RELEASE DRUG DELIVERY SYSTEM**
- **TARGETED DRUG DELIVERY SYSTEMS**

CONVENTIONAL DRUG DELIVERY SYSTEM

Conventional drug delivery system is known to provide a prompt release of drug; therefore, to attain as well as to maintain the drug concentration within the therapeutically effective range needed for treatment, it is often necessary to take these types of drug delivery system several times a day. This result in a significant fluctuation in drug levels (Chien Y.W, 1982; Jaiswal.S.B *et al*., 2007).

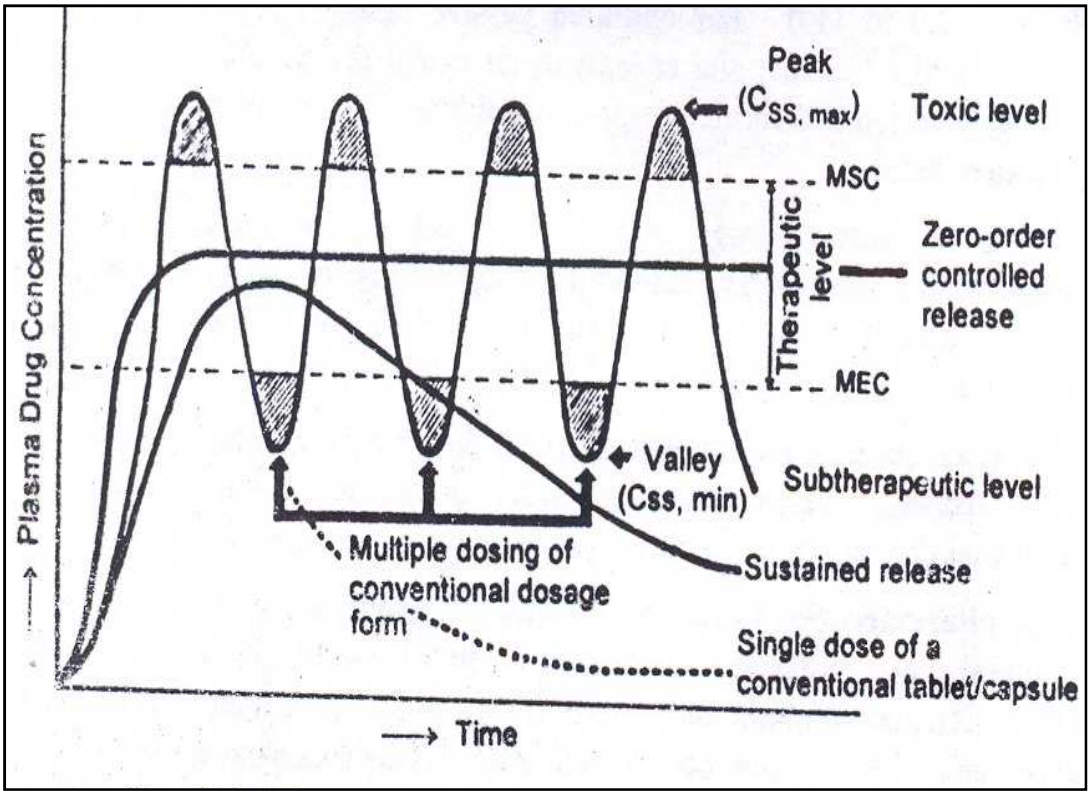


Figure 1: Plasma drug concentration-time profile for conventional dosage formulation, a sustained release formulation and a zero order controlled delivery formulation.

Drawbacks of Conventional Dosage Forms:

- ✶ Poor patient compliance
- ✶ Increased chances of missing the dose of a drug
- ✶ Shorter half life
- ✶ To attain steady-state plasma concentration is difficult.
- ✶ Fluctuations in drug levels (Shalin A. Modi *et al*., 2011; Chien Y.W, 1992).

A) SUSTAINED RELEASE DRUG DELIVERY

Sustained release drug delivery system, which means the release of active agent is slower than any conventional formulation, but is significantly affected by an external environment. The onset of its pharmacological action is delayed, and the duration of therapeutic effect is sustained. That means, to retard the release of a therapeutic agent in the systemic circulation is delayed and/or prolonged and its plasma profile is sustained (Jaiswal.S.B *et al*., 2007; Shalin A. Modi *et al*., 2011).

B) CONTROLLED RELEASE DRUG DELIVERY SYSTEM

Controlled release systems provide a release profile independent of external environment and predominantly controlled by the design of the system. It implies a predictability and reproducibility in the drug release kinetics. That means, the release of drug ingredient(s) from a controlled-release drug delivery system proceeds at a rate profile that is predictable kinetically, and also reproducible from one unit to another (Xiaoling Li *et al*., 2005; Brahmankar D.M *et al*., 1995).

The plasma level of drug should be maintained within the safe margin and effective range, for this proper and calculated dose of the drug need to be given at different time intervals by conventional dosage forms (Shalin A. Modi *et al*., 2011).

C) TARGETED DRUG DELIVERY SYSTEM

Targeted delivery refers to the systemic administration of a drug carrier with the goal of delivering the drug to specific cell types, tissues, or organs.

The distribution of other tissues seems unnecessary, and a potential cause of toxicity. Most of diseases treated by cytotoxic agents not only demand for controlled drug delivery but also the pattern of delivery is directed to be specific, precise and defined at quantitative levels.

The legend-receptor interactions are highly stereo specific. Thus ligands or receptors could be exploited for site/cell specific drug delivery quantitatively in a well defined manner.

Approaches are being adopted either to control the distribution of drug by incorporating it in a carrier or altering the structure of the drug at the molecular level, or by controlling the input of the drug into the bioenvironmental to ensure a programmed and desirable biodistribution (Vyas.S.P & Khar, 2002).

RATIONALE OF SUSTAINED, CONTROLLED AND TARGETED DRUG DELIVERY:

The drug delivery system are usually known by terms like sustained, controlled, targeted, novel, and therapeutic and programmed. However, the basic rationale for these varied delivery modules is the alteration or manipulation of pharmacokinetic and pharmacodynamic of pharmacologically active moieties. This can be achieved either by using novel delivery devices (like Liposome, Transdermal patches or Matrix or Membrane controlled devices) , or by modifying the structure in molecular level (Prodrug or Chemical delivery system) and/or physiological parameters inherent by route of administration selected (like rectal route to avoid first pass metabolism). A drug delivery system may be thought of as one in which three components are included: the drug input

function: the pharmacokinetic responses (metabolism): and the pharmacodynamic responses (therapeutic and side effects) (Xiaoling Li *et al*., 2005; Brahmankar D.M *et al*., 2002).

It is important to critically evaluate different terms used under broad category of novel drug delivery systems:

- ✶ Sustained or controlled drug delivery systems provide drug action at a predetermined rate by providing a prolonged or constant (zero-order) release respectively, at therapeutically effective levels in the circulation.
- ✶ Localized drug delivery devices through spatial or temporal control of drug release (usually rate-limiting) in the vicinity of the target.
- ✶ Rate-preprogrammed drug delivery systems, by the release of drug molecules by system design, which controls the molecular diffusion of drug molecules. Fick's laws of diffusion are followed.
- ✶ Targeted drug delivery by using carriers either meant for passive preprogrammed or active preprogrammed or self-programmed approach or usually appended with suitable site-directing molecules which recognize their receptor or carbohydrate determinants at the target.

RECENT DEVELOPMENTS

Controlled-released formulations have been widely developed and marketed over the past 30years under various terms such as sustained release, prolonged-release, timed-release, or other similar names that are often ill-defined and misleading.

Recently, a number of novel drug delivery systems that uses unique concepts have been studied intensively. Some of the strategies include targeted delivery, self-regulated release, biofeedback mechanisms, and drug attached to biological carriers (Vyas.S.P & Khar, 2002; Xiaoling Li *et al.,* 2005).

Controlled-release formulations can be designed for any route of administrations as follows:

- Oral
- Parenteral
- Implants
- Transdermal
- Other routes: ocular, nasal, vaginal, etc.

The development of improved controlled-release and novel drug delivery systems will have significant implications for achieving more effective drug therapy.

The most preferred route of drug administration for systemic delivery of drugs is orally**.** More than 50% of drug delivery systems available in the market are oral drug delivery systems. These systems have the obvious advantages of case of administration and patient acceptance. Several oral drug delivery technologies have come and gone, and new systems still emerge even today.

One would always like to have ideal drug delivery systems that will possess two main properties,

1. It will be a single dose for the whole duration of treatment
2. It will deliver the active drug directly at the site of action.

It offers advantages like,

- ✶ Patient compliance
- ✶ Flexibility in formulation
- ✶ Ease of administration

Reasons for Interest in New DDS

- ✶ Improving conventional dosage forms
- ✶ Exclusivity for existing drugs
- ✶ High cost for developing new drugs
- ✶ Delivery of bioengineered compounds
- ✶ Enhanced efficacy and safety

Some of the potential benefits and drawbacks of controlled-release and novel drug delivery systems are as follows:

Potential Benefits of Novel Drug Delivery System

- ✶ Convenience in dosing
- ✶ Higher patient compliance
- ✶ Better utilization of drugs
- ✶ Reduced adverse effects
- ✶ Improved efficacy

Potential Problems of Novel Drug Delivery

- ✶ Delivery of drugs to the target tissues/organs
- ✶ Extravasations of drugs/carriers in the tissues/organs
- ✶ Liberation of drugs from the carrier

- Penetration into specific cells/cell components
- Control of residence time at the receptor site.

ORAL CONTROLLED RELEASE FORMULATIONS

Oral route has been the commonly selected and most suitable for the drug delivery. Oral route of administration has more attention in the pharmaceutical field because of the more flexibility in the designing of dosage form than other routes of drug delivery (Stanley S.Davies *et al*., 2005; Shalin A. Modi *et al*., 2011).

The oral controlled drug delivery systems are mostly solids and based on diffusion, dissolution or combination of both mechanisms in the control of release rate of drug.

Novel oral drug delivery systems are broadly classified into two categories as they may control release dosage forms as well as targeting dosage forms. General controlled manner in the GIT for systemic uptake and no particular area of GIT specified. In contrast, targeted preparations are releasing the drug in a specified area or tissue of the GI (e.g. floating drug delivery system).

Targeting systems are either releasing drug in controlled manner or in one burst at the specific area. The goal of a targeted oral drug delivery system (TODDS) is to achieve better therapeutics success compared to conventional dosage form. This can be achieved by improving the pharmacokinetic profile, patient convenience and compliance in therapy (Stanley S.Davies *et al*., 2005).

Advantages of TODDS

- ✶ Reduced dosing frequency
- ✶ Better patient convenience and compliance
- ✶ Reduced GI side effects and other toxic effects.
- ✶ Less fluctuating plasma drug level
- ✶ More uniform drug effect
- ✶ Less total dose
- ✶ Better stability of the drug (Brahmankar D.M *et al*., 1995; Vyas S.P & Khar, 2002).

Disadvantages of TODDS:

- ✶ Higher cost
- ✶ Relatively poor *in vitro-in vivo* correlation
- ✶ Possible dose dumping
- ✶ Reduced potential for dose change or withdrawal in the event of toxicity (Brahmankar D.M *et al*., 1995).

Targeting of drugs through oral route involves control of time of release or location of release. On the basis of environmental, anatomical and physiological factors these drug delivery system can be classified with respect to target site as follows:

- ✶ Systems targeted to stomach/duodenum
- ✶ Systems targeted to small intestine
- ✶ Systems targeted to large intestine/colon
- ✶ Systems targeted to lymphatic.

ORAL DIFFUSION-CONTROLLED SYSTEM

The basic concepts of oral controlled release dosage forms can be defined based on release-profile characteristic or the underlying release- controlling mechanism. Two distinct drug release profiles, extended and delayed release, are achievable, and they can be used in various combinations to provide the desired release rate. Three delivery systems dominate today's market of oral CR products:

- ✶ Matrix systems,
- ✶ Reservoir systems and
- ✶ Osmotic systems.

Release mechanisms from these dosage forms, diffusion plays a key role in both matrix and reservoir systems, whereas osmotic pressure is the predominant mechanism of drug release from osmotic systems and could also play a role in a reservoir system (Shalin A. Modi *et al*., 2011).

A) Matrix systems

A matrix system consists of active and inactive ingredients that are homogeneously mixed in the dosage form. Matrix systems divide into two categories, based on rate-controlling materials (Shalin A. Modi *et al*., 2011).

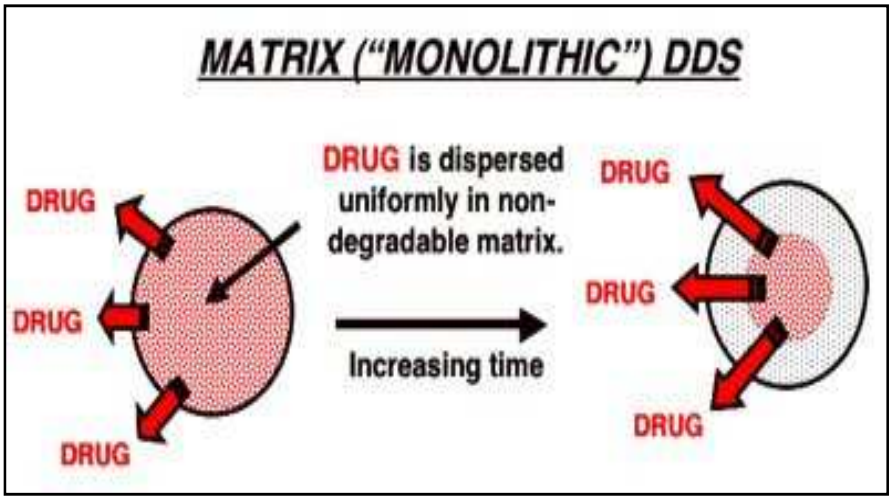


Figure 2: Matrix ("Monolithic") DDS

- ✶ **Hydrophobic matrix systems**
- ✶ **Hydrophilic matrix systems**

1. Hydrophobic matrix systems

This is the only system where use of a polymer is not essential to provide controlled drug release, although insoluble polymers have been used. As the term suggests, the primary rate-controlling components of a hydrophobic matrix are water insoluble in nature. These ingredients include waxes, glycerides, fatty acids, and polymeric materials such as ethyl cellulose and methacrylate copolymers. To modulate drug release, it is necessary to incorporate soluble ingredients such as lactose into the formulation.

The presence of insoluble ingredients in the formulations helps to maintain the physical dimension of a hydrophobic matrix during drug release. Diffusion of the active form from the system is the release mechanism. Very often, pores form within a hydrophobic matrix as a result of the release of the active ingredient. Hydrophobic matrix

systems generally are not suitable for insoluble drugs because the concentration gradient is too low to render drug release.

2. Hydrophilic matrix systems

The primary rate-controlling ingredients of a hydrophilic matrix are polymers that would swell on contact with the aqueous solution and form a gel layer on the surface of the system.

Drugs release from hydrophilic matrices is by polymer dissolution (erosion) and diffusion of drug molecules across the gel layer have been identified as the rate-controlling mechanisms.

The model semi empirical "exponent equation" has been used widely to differentiate the contributions of both mechanisms:

$$Q_t = kt^n$$

Where Q_t is amount Q in time t, *n* is a diffusion exponent, and *k* is a kinetic constant. If diffusion dominates polymer erosion, the value of *n* would approach 0.5. On the other hand, for erosion-controlled formulations, *n* would approach the value of unity. Under an "anomalous" condition, the value of *n* falls in between 0.5 and 1 when both diffusion and erosion play roles.

More recently, a "spaghetti" model (Figure 3) for a swollen matrix was developed to provide mechanistic understanding of the complex release process. This model treats polymer erosion as diffusion of polymer across a "diffusion layer" adjacent to the gel layer. Thus two competitive diffusion processes contribute to overall drug release: diffusion of polymer across the diffusion layer and diffusion of drug across the gel layer.

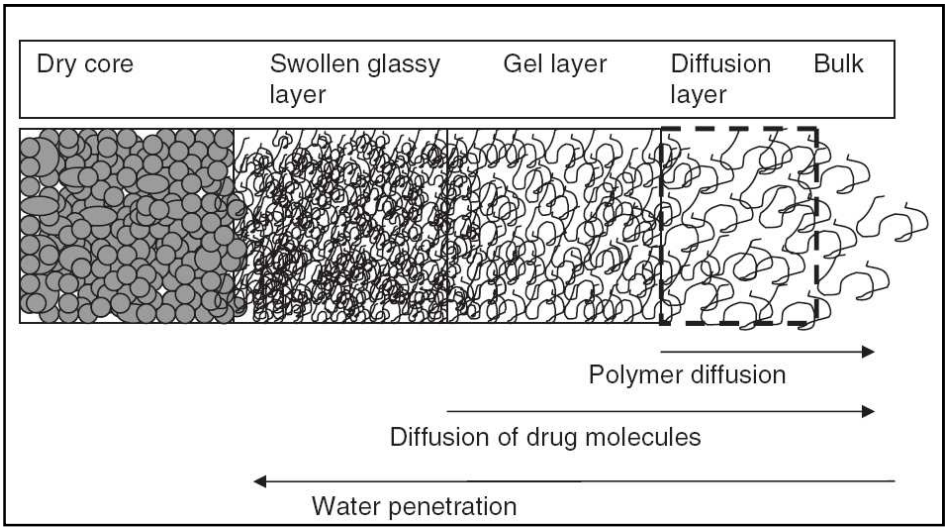


Figure 3: Spaghetti model for a swollen matrix

For very soluble compounds, diffusion of drug molecules is the dominant mechanism of release, and the role of polymer erosion is limited in modulating drug release. Thus, developing a hydrophilic matrix for highly soluble drugs that requires prolonged release (e.g., >12 h) can be challenging. On the other hand, release of less soluble drugs from hydrophilic matrices is expected to be slow because both polymer dissolution and drug diffusion play key roles.

The polymers used in the preparation of hydrophilic matrices,

1. Cellulose derivates
2. Non-cellulose natural or semi synthetic polymers
3. Polymers of acrylic acid.

B) Reservoir Devices

Reservoir devices are those in which a core of drug is surrounded by polymeric membrane. The nature of membrane determines the rate of release of drug from system.

The process of diffusion is generally described by a series of equations governed by Fick's first law of diffusion (Shalin A. Modi *et al*., 2011).

$$J = -D (dc/ dx) \qquad (1)$$

Where,

- J = flux of drug across the membrane given in units of amount / area time.
- D = diffusion coefficient of drug in membrane in units of area / time.

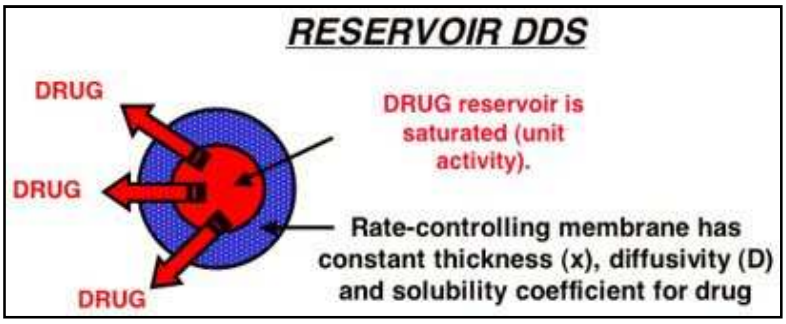


Figure 4: Reservoir DDS

This is reflecting to drug molecule's ability to diffuse through the solvent and is dependent on the factors as molecular size and charge.

- ✶ dc/ dt = represents rate of change in concentration C relative to a distance X in the membrane.

The law states that amount of drug passing across a unit area, is proportional to the concentration difference across that plane.

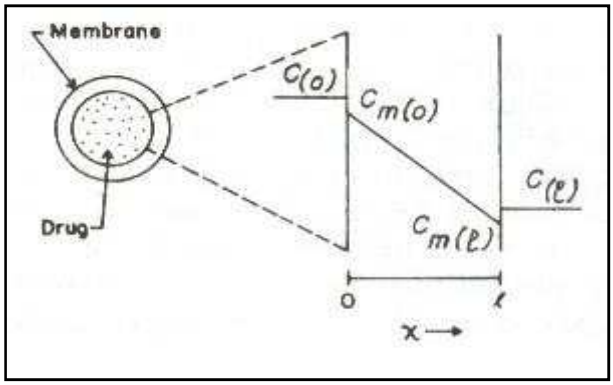


Figure 5: Schematic representation of reservoir diffusion device C_m (o), and C_m (d) represent concentration of drug inside surfaces of membrane and C (o) & C (d) represents concentration in adjacent regions.

If it is assumed that the drug on the both side of membrane is in equilibrium with its respective membrane surface which in equilibrium between the membrane surfaces and their bathing solutions as shown in Figure 5. Therefore the concentration just inside the membrane surface can be related to the concentration in the adjacent region by following expression.

$$\mathbf{K = C_m\ (o)\ /C\ (d) \quad at\ X = o} \qquad (2)$$

$$\mathbf{K = C_m\ (d)\ /\ C\ (d) \quad at\ X = d} \qquad (3)$$

Where,

K = Partition coefficient.

If we consider K & D are constants then equation (1) becomes,

$$\mathbf{J = D\ K\ \Delta C/d} \qquad (4)$$

Where,

- ✶ Δc is the concentration difference across the membrane and d is path length of diffusion.

The simplest system to consider is that of slab, where drug release is from only one surface as shown Figure 6 in this case equation (4) becomes

$$dMt/dt = ADK\,\Delta C/d \qquad (5)$$

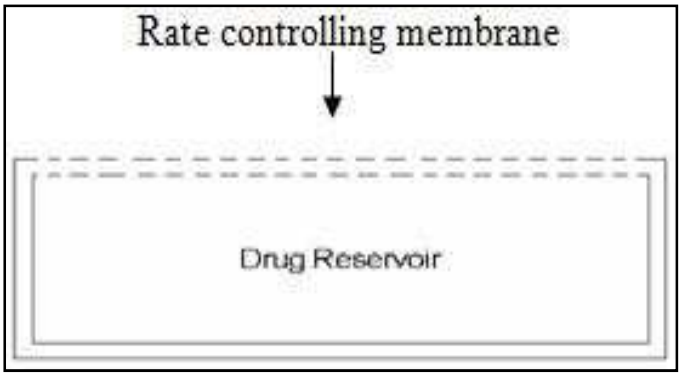


Figure 6: Diagrammatic representation of slab configuration of reservoir diffusion system.

Non permeable polymer shell

Where,

- ✶ Mt = Mass of drug released after time t.
- ✶ dMt/dt =Steady state drug release rate of time 't'.
- ✶ A=surface area of device.

If variables of right side of equation remain constant, then left side of equation represents release rate of system, a true controlled release system with a zero-order release rate.

A constant effective area of diffusion, diffusional path length, concentration difference, and diffusion coefficient are required to obtain a release rate that is constant. Reservoir diffusional systems have several advantages over conventional dosage forms. They can after zero order release of drug, kinetics of which can be controlled by changing the characteristics of the polymer to meet the particular drug and therapy conditions.

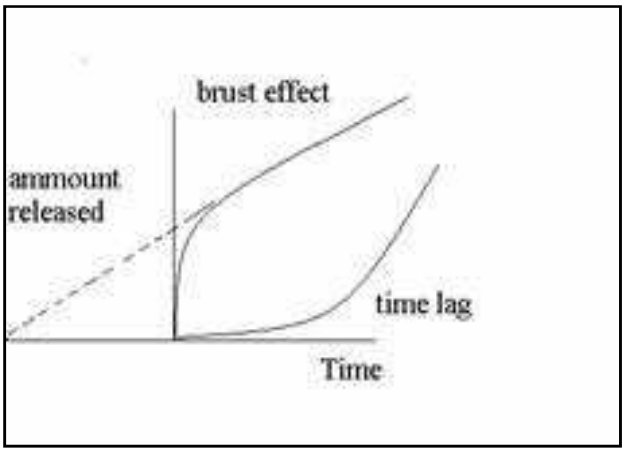


Figure 7: Plot showing approach to steady state for reservoir device that has been stored for an extended period (the burst effect curve) and for device that has been freshly made (the time lag curve)

Common methods used to develop reservoir type of devices include micro encapsulation of drug particles and press coating of tablets containing drug cores. In most cases particles coated by microencapsulation form a system where the drug is contained in the coating film as well as in the core of micro capsule. The drug release generally involves combination of dissolution and diffusion with dissolution being process that controls the release rate. If encapsulating material is selected properly will be the

controlling process. Some materials such as membrane barrier coat alone or in combination, are hardened gelatin, methyl or methylcellulose, polyhydroxymethacrylate hydroxypropylmethylcellulose, polyvinyl acetate & various waxes.

ORAL DISSOLUTION CONTROLLED SYSTEM

These types of systems are easiest to design. The drug present in such system may be the one (Shalin A. Modi *et al*., 2011):

1. Inherently slow dissolution rate e.g. Digoxin
2. Slow dissolving form, when it comes contact with GI fluids
3. High aqueous solubility and dissolution rate.

Dissolution-controlled release can be obtained by slowing the dissolution rate of a drug in the GI medium, incorporating the drug in an insoluble polymer material of varying thickness. The rate limiting step for dissolution of a drug is the diffusion across the aqueous boundary layer. The solubility of the drug provides the source of energy for drug release, which is countered by the stagnant-fluid diffusional boundary layer. The rate of dissolution can be approximated by,

$$dm/dt = Ads/h$$

Where,

- ✶ S = Aqueous solubility of the drug
- ✶ A = Surface area of the dissolving particle of tablet
- ✶ D = Diffusivity of the drug

- H = Thickness of the boundary layer

There are two drug delivery system in dissolution controlled,

1. Matrix dissolution controlled systems
2. Reservoir dissolution controlled systems.

A) Matrix dissolution controlled systems:

The drug is homogeneously dispersed throughout the rate controlling medium; this system is also called as monolith system. The rate of dissolution fluid penetration into the matrix by altering the porosity of tablet, decreasing its wettability or by itself getting dissolved at a slower rate.

B) Reservoir dissolution controlled systems:

The drug particles are coated or encapsulated by one of the several microencapsulation techniques slowly dissolving materials like cellulose and PEG. The dissolution rate of coat depends upon the solubility and thickness of the coating.

Classification of oral controlled drug delivery system

1. **Continuous release system**

- Dissolution controlled release system
- Diffusion controlled release system
- Diffusion and dissolution controlled release system.
- Ion exchange resin drug complexes
- Slow dissolving salt and complexes

- ✶ pH independent formulations.
- ✶ Osmotic pressure controlled systems
- ✶ Hydrodynamic pressure controlled systems.

2. Delayed transit and continuous release systems

- ✶ Altered density system.
- ✶ Mucoadhesive system.
- ✶ Size based systems.

3. Delayed Release system

- ✶ Intestinal release system.
- ✶ Colonic release system.

Factors influencing the design and performance of controlled drug delivery system

- ✶ Biopharmaceutical characteristic of the drug
- ✶ Molecular weight of the drug
- ✶ Aqueous solubility of the drug
- ✶ Apparent partition coefficient
- ✶ Drug pka and ionization physiological pH
- ✶ Drug stability
- ✶ Mechanism and site of absorption
- ✶ Route of administration.
- ✶ Pharmacokinetic characteristic of the drug
- ✶ Absorption rate
- ✶ Elimination half life
- ✶ Rate of metabolism

- Dosage form index
- Pharmacodynamic characteristic of the drug
- Therapeutic range
- Therapeutic index
- Plasma–concentration–response relationship (Jain N.K, 2002; Gilbert S. Banker; Lee V.H., Robinson J.R).

Advantages of controlled drug delivery systems

- Improved patient convenience and compliance
- Reduction in fluctuation in steady state levels.
- Increased safety margin of high potency drugs.
- Reduction in dose.
- Reduction in health care cost.
- Total dose is low.
- Reduced GI side effects.
- Reduced dosing frequency.
- Better patient acceptance and compliance.
- Less fluctuation at plasma drug levels.
- More uniform drug effect
- Improved efficacy/safety ratio.
- Dose dumping.
- Reduced potential for accurate dose adjustment.
- Need of additional patient education (Jain N.K, 2002; Vyas S.P & Khar, 2002).

Disadvantages of controlled drug delivery systems

- ✶ Decreased systemic availability.
- ✶ Poor *invitro-in vivo* correlations.
- ✶ Chances of dose dumping.
- ✶ Dose withdrawal is not possible.
- ✶ Higher cost of formulation.

CHAPTER II

GASTRO RETENTIVE DRUG DELIVERY SYSTEM-REVIEW

GASTRO RETENTIVE DRUG DELIVERY SYSTEM:

Oral administration is the most convenient and preferred means of any drug delivery to the systematic circulation. Oral controlled release drug delivery have recently been of increasing interest in pharmaceutical field to achieve improved therapeutic advantages, such as ease of dosing administration, patient compliance and flexibility in formulation. Drugs that are easily absorbed from gastrointestinal tract (GIT) and have short half-lives are eliminated quickly from the systemic circulation. Frequent dosing of these drugs is required to achieve suitable therapeutic activity (Amit Kumar Nayak *et al.,* 2010).

To avoid this limitation, the development of oral sustained-controlled release formulations is an attempt to release the drug slowly into the gastrointestinal tract (GIT) and maintain an effective drug concentration in the systemic circulation for a long time. After oral administration, such a drug delivery would be retained in the stomach and release the drug in a controlled manner, so that the drug could be supplied continuously to its absorption sites in the gastrointestinal tract (GIT).

These drug delivery systems suffer from mainly two adversities: the short gastric retention time (GRT) and unpredictable short gastric emptying time (GET), which can result in incomplete drug release from the dosage form in the absorption zone (stomach or upper part of small intestine) leading to diminished efficacy of administered dose. To formulate a site-specific orally administered controlled release dosage form, it is desirable to achieve a prolong gastric residence time by the drug delivery. Prolonged gastric retention improves bioavailability, increases the duration of drug release, reduces drug

waste, and improves the drug solubility that are less soluble in a high pH environment. Also prolonged gastric retention time (GRT) in the stomach could be advantageous for local action in the upper part of the small intestine (e.g. treatment of peptic ulcer, etc) (Amit Kumar Nayak *et al.,* 2010).

Gastro retentive drug delivery is an approach to prolong gastric residence time, thereby targeting site-specific drug release in the upper gastrointestinal tract (GIT) for local or systemic effects. Gastro retentive dosage forms can remain in the gastric region for long periods and hence significantly prolong the gastric retention time (GRT) of drugs. Over the last few decades, several gastro retentive drug delivery approaches being designed and developed, including: High density (sinking) systems that is retained in the bottom of the stomach, Low density (floating) systems that causes buoyancy in gastric fluid, mucoadhesive systems that causes bioadhesion to stomach mucosa, unfoldable, extendible, or swellable systems which limits emptying of the dosage forms through the pyloric sphincter of stomach, super porous hydrogel systems, magnetic systems etc. The current review deals with various gastro retentive approaches that have recently become leading methodologies in the field of site-specific orally administered controlled release drug delivery systems (Amit Kumar Nayak *et al.,* 2010).

BIOLOGICAL ASPECTS OF GRDFs

Anatomy of the gastrointestinal tract:

The gastrointestinal tract is divided into three main regions namely:

- ✶ Stomach.
- ✶ Small intestine (Duodenum, Jejunum and Iieum).

- Large intestine.

The GIT is a muscular tube, from the mouth to the anus, which functions to take in nutrients and eliminate waste by secretion, motility, digestion, absorption and excretion, which are known as physiological processes (Shiv Kumar Yadav *et al*., 2011).

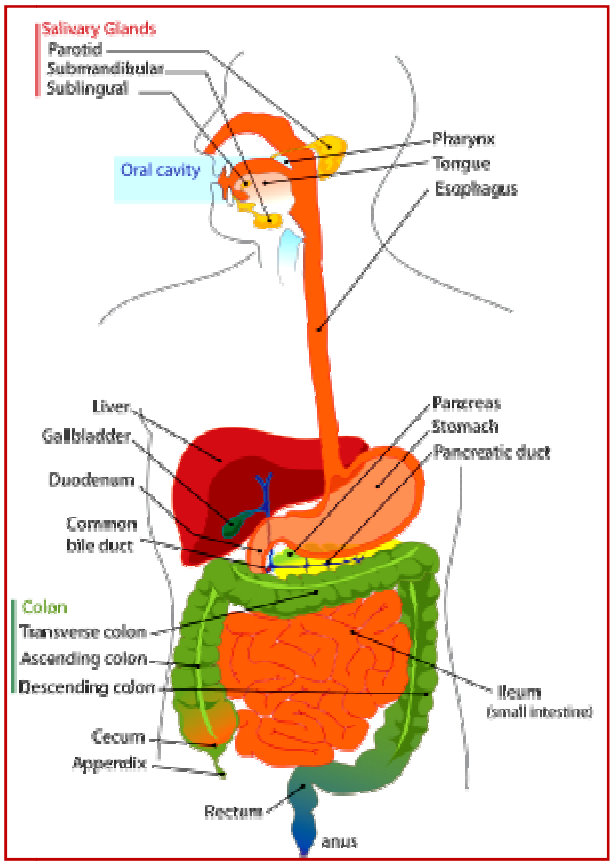


Figure 1: Anatomy of Gastro Intestinal Tract

Basic gastrointestinal tract physiology:

The stomach is an expanded section of the digestive tube between the oesophagus and small intestine. The wall of the stomach is structurally similar to the other parts of the digestive tube, with the exception that stomach has an extra, oblique layer of smooth muscle inside the circular layer, which aids in the performance of complex grinding

motions. In the empty state, the stomach is contracted and its mucosa and sub mucosa are thrown up into distinct folds called rugae (Natasha Sharma *et al*., 2011).

The stomach is anatomically divided into three parts,

- ✶ Fundus
- ✶ Body
- ✶ Antrum (or pylorus).

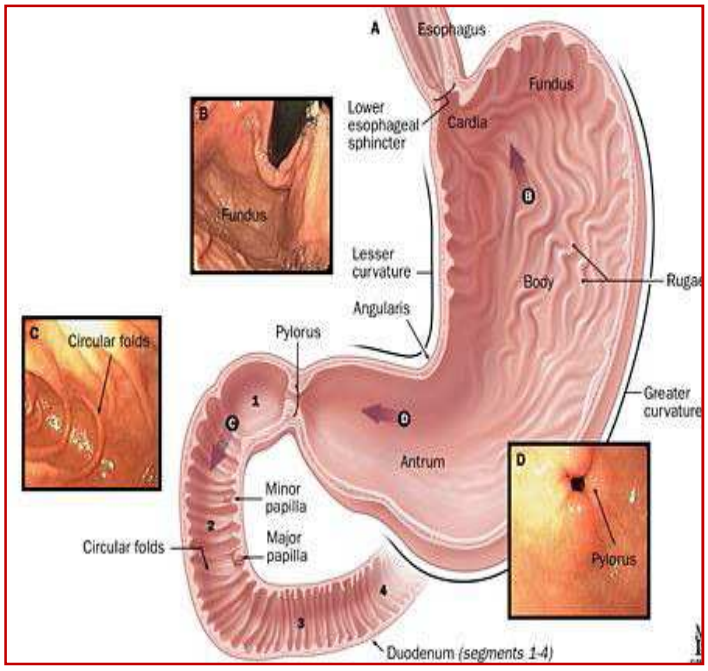


Figure 2: Physiology of stomach

There are images to four major types of secretary epithelial cells that cover the surface of the stomach and extend down into gastric pits and glands

- ✶ **Mucous cells**: secrete alkaline mucus that protects the epithelium against shear stress and acid.
- ✶ **Parietal cells**: secrete hydrochloric acid.
- ✶ **Chief cells**: secrete pepsin, a proteolytic enzyme.
- ✶ **G cells**: secrete the hormone gastrin.

The contraction of gastric smooth muscle serves two basic functions:

- ✶ Ingested food is crushed, ground, mixed and liquefying to form Chyme.
- ✶ Chyme is forced through the pyloric canal into the small intestine, a process called gastric emptying.

The proximal stomach, made up of the fundus and body regions, serves as a reservoir for ingested materials while the distal region (antrum) is the major site of mixing motions, acting as a pump to accomplish gastric emptying. Gastric emptying occurs during fasting as well as fed states. The pattern of motility is however distinct in the 2 states. During the fasting state an interdigestive series of electrical events take place, which cycle both through stomach and intestine every 2 to 3 hours. This is called the interdigestive myloelectric cycle or migrating myloelectric cycle (MMC), which is further divided into following 4 phases as described by Wilson and Washington (Neha Narang *et al*., 2011).

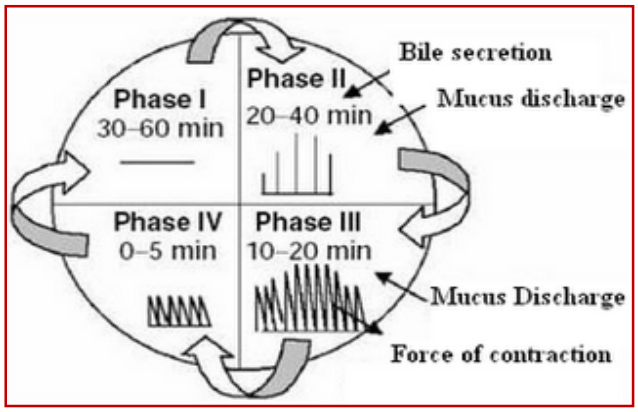


Figure 3: Schematic representation of Interdigestive Motility

Table1: Four phases in migrating myoelectric complex (MMC)
(Shweta Arora *et al*., 2005)

Phase I	It is a quiescent period lasting from 30 to 60 minutes with no contractions.
Phase II	It consists of intermittent contractions that gradually increase in intensity as the phase progresses, and it lasts about 20 to 40 minutes. Gastric discharge of fluid and very small particles begins later in this phase.
Phase III	This is a short period of intense distal and proximal gastric contractions (4–5 contractions per minute) lasting about 10 to 20 minutes; these contractions, also known as ‘‘House-keeper wave,’’ sweep gastric contents down the small Intestine.
Phase IV	This is a short transitory period of about 0 to 5 minutes, and the contractions dissipate between the last part of phase III and quiescence of phase I.

Need for gastroretention

- ✶ Drugs that are absorbed from the proximal part of the gastrointestinal tract (GIT).
- ✶ Drugs that are less soluble or that degrade at the alkaline pH.
- ✶ Drugs that are absorbed due to variable gastric emptying time.
- ✶ Local or sustained drug delivery to the stomach and proximal small intestine to treat certain conditions.
- ✶ Treatment of peptic ulcers caused by H.Pylori infections (Amit Kumar Nayak *et al*., 2010).

POTENTIAL DRUG CANDIDATES FOR GASTRORETENTIVE DRUG DELIVERY SYSTEMS

- ✶ Drugs those are locally active in the stomach.

- Drugs that have narrow absorption window in gastrointestinal tract (GIT)
- Drugs those are unstable in the intestinal or colonic environment
- Drugs that disturb normal colonic microbes
- Drugs that exhibit low solubility at high pH values (Amit Kumar Nayak *et al*., 2010)

DRUGS THOSE ARE UNSUITABLE FOR GASTRORETENTIVE DRUG DELIVERY SYSTEMS

- Drugs that have very limited acid solubility e.g. Phenytoin etc.
- Drugs that suffer instability in the gastric environment e.g. Erythromycin etc.
- Drugs intended for selective release in the colon e.g. 5- amino salicylic acid and corticosteroids etc (Amit Kumar Nayak *et al*., 2010).

Formulation aspects for GRDDS

- It must be effective retention in the stomach to suit for the clinical demand.
- It must be convenient for intake to facilitate patient compliance.
- It must have sufficient drug loading capacity and control drug release profile.
- It must have full degradation and evacuation of the system once the drug release is over.
- It should not have effect on gastric motility including emptying pattern.
- It should not have other local adverse effects (Vinod K.R. *et al.,* 2010)

Factors affecting gastric retention

The gastric retention time (GRT) of dosage form is controlled by several factors that affect their efficacy as a gastro retentive system (Vinod K.R. *et al.,* 2010; Vaishali Sharma *et al*., 2011).

1. **Density:** Gastric retention time (GRT) is a function of buoyancy of dosage form that is dependent on the density.
2. **Size:** Dosage form units with a diameter of more than 7.5 mm are reported to have an increased GRT compared with those with a diameter of 9.9 mm.
3. **Shape:** Tetrahedron and ring shaped devices with a flexural modulus of 48 and 22.5 kilo pounds per square inch (KSI) are reported to have better GRT 90% to 100% retention at 24 hours compared with other shapes.
4. **Single or Multiple unit formulation:** Multiple unit formulations show a more predictable release profile and insignificant impairing of performance due to failure of units, allow co-administration of units with different release profiles or containing incompatible substances and permit a larger margin of safety against dosage form failure compared with single unit dosage forms.
5. **pH (Hydrogen Ion Concentration)** – The mean pH (+ S.D.) along the G.I. Tract in normal subjects are given by:

Region	Mean pH
Stomach	1.8 + 0.6
Proximal Small Intestine	6.6 + 0.5
Mid Small Intestine	7.4 + 0.4
Distal Small Intestine	7.5 + 0.5
Right Colon	6.3 + 0.6
Mid Colon	6.6 + 0.8
Left Colon	7.1 + 0.7

The pH of the stomach in fasting state is ~1.5 to 2.0 and in fed state is 2.0 to 6.0. A large volume of water administered with an oral dosage form raises the pH of stomach contents to 6.0 to 9.0. Stomach doesn't get time to produce sufficient acid when the liquid empties the stomach.

The various pH of the gastro intestinal tract is shown in Figure 4.

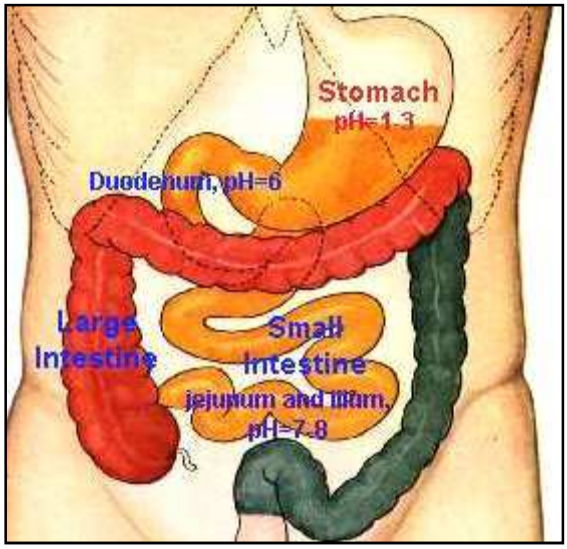


Figure 4: pH of Gastro Intestinal Tract

6. **Fed or unfed state:** Under fasting conditions, the GI motility is characterized by periods of strong motor activity or the migrating myoelectric complex (MMC) that occurs every 1.5 to 2hrs. The MMC sweeps undigested material from the stomach and, if the timing of administration of the formulation coincides with that of the MMC, the GRT of the unit can be expected to be very short. However, in the fed state, MMC is delayed and GRT is considerably longer.
7. **Nature of meal:** Feeding of indigestible polymers or fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging drug release.

8. **Caloric content:** GRT can be increased by 4 to 10 hours with a meal that is high in proteins and fats.
9. **Frequency of feed:** The GRT can increase by over 400 minutes when successive meals are given compared with a single meal due to the low frequency of MMC.
10. **Gender:** Mean ambulatory GRT in males (3.4±0.6 hours) is less compared with their age and race matched female counterparts (4.6±1.2 hours), regardless of the weight, height and body surface.
11. **Age:** Elderly people, especially those over 70, have a significantly longer GRT.
12. **Posture:** GRT can vary between supine and upright ambulatory states of the patient.
13. **Concomitant drug administration:** Anticholinergics like atropine, propantheline, opiates like codeine and prokinetic agents like Metoclopramide and Cisapride, can affect floating time.
14. **Biological factors:** Diabetes and Crohn's disease etc.

Approaches to Gastric retention

Various approaches have been pursued to increase the retention of an oral dosage form in the stomach. These systems include (Vinod K.R. *et al.,* 2010; Vaishali Sharma *et al*., 2011),

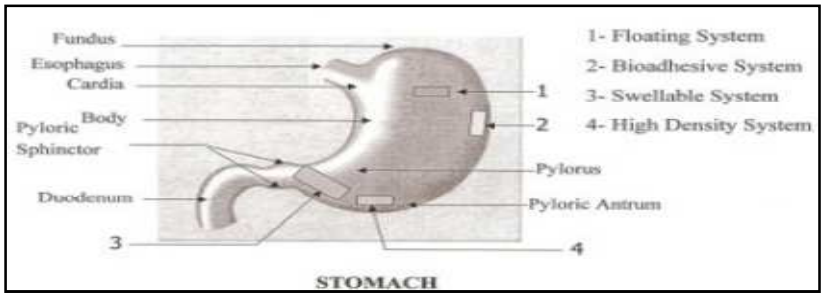
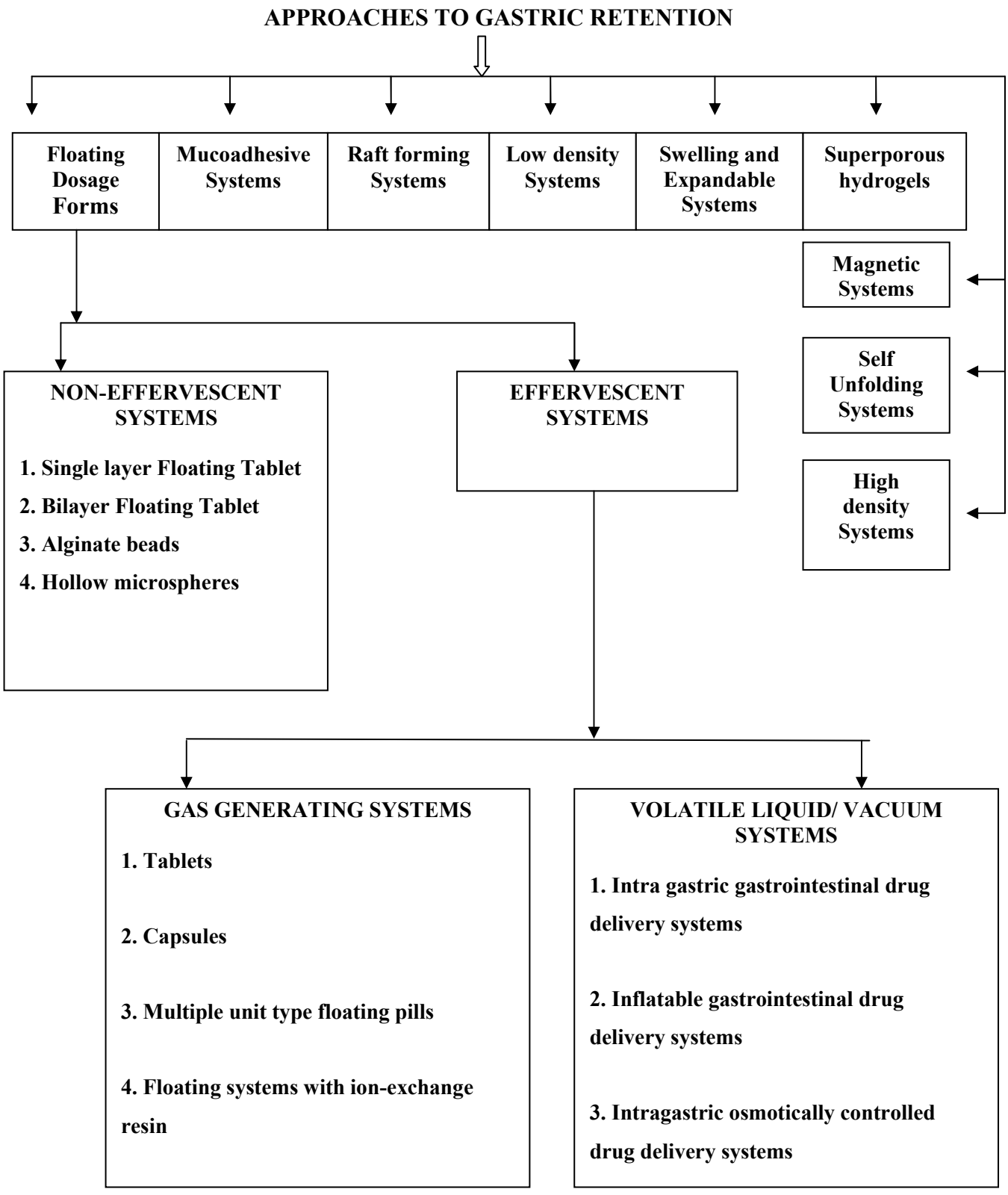


Figure 5: *In vivo* picturisation of various gastro retentive formulations

Figure 6: Schematic representation of various Gastro retentive formulations



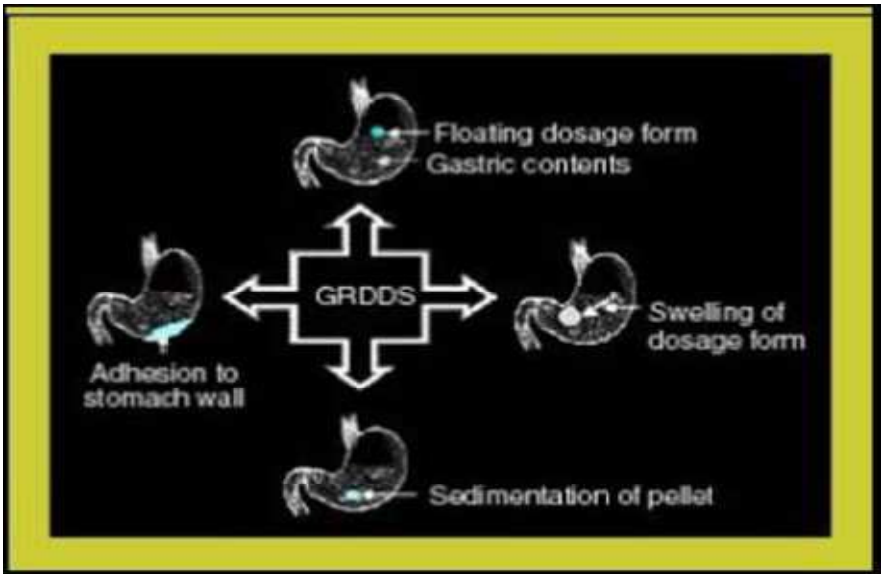


Figure 7: APPROACHES TO GASTRIC RETENTION

1. High density (sinking) system or non- floating drug delivery system:

This approach involves formulation of dosage forms with the density that must exceed density of normal stomach content (~ 1.004 gm/cm^3). These formulations are prepared by coating drug on a heavy core or mixed with inert materials such as iron powder, barium sulphate, zinc oxide and titanium oxide etc. The materials increase density by up to 1.5- 2.4 gm/cm^3. A density close to 2.5 gm/cm^3 seems necessary for significant prolongation of gastric residence time. But, effectiveness of this system in human beings was not observed and no system has been marketed (Amit Kumar Nayak *et al*., 2010).

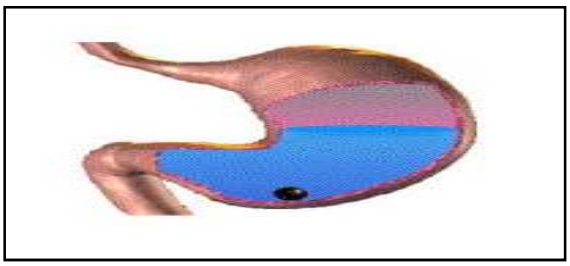


Figure 8: High density systems

2. Floating system or Low density system:

Floating Drug Delivery Systems (FDDS) have a bulk density lower than gastric fluids and thus remain buoyant in the stomach, (Figure 9), for a prolonged period of time, without affecting the gastric emptying rate and the drug is released slowly at a desired rate from the system, results in an increase in the gastric residence time and a better control of fluctuations in the plasma drug concentrations and after complete release of the drug, the residual system is emptied from the stomach (Neha Narang *et al*., 2011).

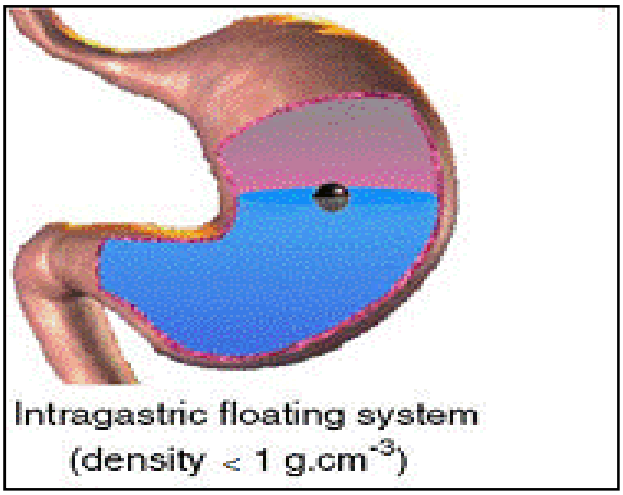


Figure 9: Low density systems (Floating system)

3. Expandable, unfoldable and swellable systems:

These systems are also called as "Plug type system", since they exhibit tendency to remain logged in the pyloric sphincters. These polymeric matrices remain in the gastric cavity for several hours even in fed state. By selection of polymer with the proper molecular weight and swelling properties controlled and sustained drug release can be achieved. Upon coming in contact with gastric fluid, the polymer imbibes water and swells.

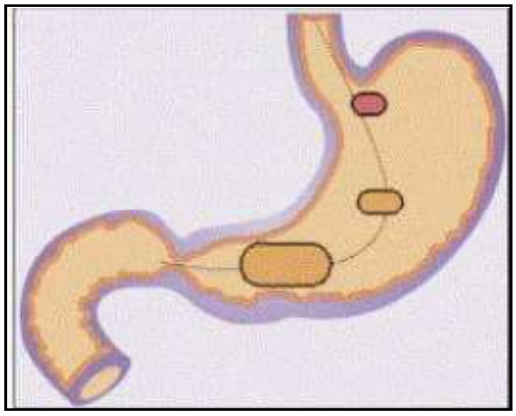


Figure 10: Swellable tablet in stomach

A dosage form in the stomach will withstand gastric transit if it bigger than pyloric sphincter. However, the dosage form must be small enough to be swallowed, and must not cause gastric obstruction either singly or by accumulation. Thus, their configurations are required to develop an expandable system to prolong gastric retention time (GRT),

- ✶ A small configuration for oral intake,
- ✶ An expanded gastro retentive form, and
- ✶ A final small form enabling evacuation following drug release from the device.

Thus, gastroretentivity is improved by the combination of substantial dimension with high rigidity of dosage form to withstand peristalsis and mechanical contractility of the stomach.

Unfoldable and Swellable systems have been investigated and recently tried to develop an effective gastro retentive drug delivery. Unfoldable systems are made of biodegradable polymers. They are available in different geometric forms like tetrahedron, ring or planner membrane (4 - label disc or 4 - limbed cross form) of bio erodible polymer compressed within a capsule which extends in the stomach. Swellable systems

are also retained in the gastro intestinal tract (GIT) due to their mechanical properties. The swelling is usually results from osmotic absorption of water and the dosage form is small enough to be swallowed by the gastric fluid (Amit Kumar Nayak *et al*., 2010).

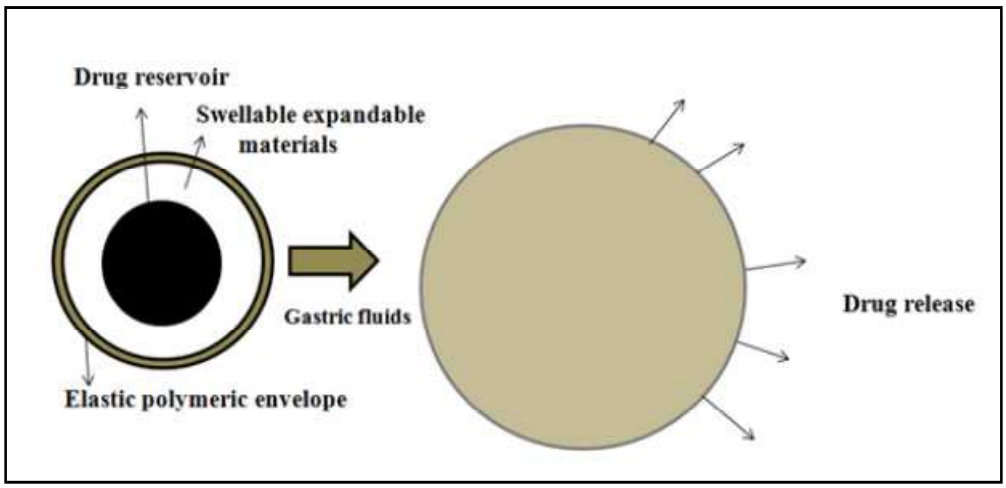


Figure 11: Drug release from swellable systems

Expandable systems have some drawbacks like problematical storage of much easily hydrolysable, biodegradable polymers relatively short-lived mechanical shape memory for the unfolding system most difficult to industrialize and not cost effective. Again, permanent retention of rigid, large single-unit expandable drug delivery dosage forms may cause brief obstruction, intestinal adhesion and gastropathy.

4. Bioadhesive or Mucoadhesive drug delivery systems:

Bioadhesive drug delivery systems are used as materials commonly used for bioadhesion are poly acrylic acid, chitosan, cholestyramine, sodium alginate, hydroxypropyl methylcellulose (HPMC), sucralfate, tragacanth, dextrin, polyethylene glycol (PEG) and polylactic acids etc. Even though some of these polymers are effective at producing bioadhesive, it is very difficult to maintain it effectively because of the rapid turnover of mucus in the gastrointestinal tract (GIT) (Amit Kumar Nayak *et al*., 2010; Sunil Kumar *et al*., 2012).

1. Hydration-mediated adhesion:

Certain hydrophilic polymers tend to imbibe large amount of water and become sticky, thereby acquiring bio adhesive properties (Anand S. Surana *et al*., 2010).

2. Bonding-mediated adhesion:

The adhesion of polymers to a mucus/epithelial cell surface involves various bonding mechanisms, including physical-mechanical bonding and chemical bonding. Physical-mechanical bonds can result from the insertion of the adhesive material into the folds or crevices of the mucosa. Chemical bonds may be either covalent (primary) or ionic (secondary) in nature. Secondary chemical bonds consist of dispersive interactions (i.e., Vander Waals interactions) and stronger specific interactions such as hydrogen bonds. The hydrophilic functional groups responsible for forming hydrogen bonds are the hydroxyl and carboxylic groups (Anand S. Surana *et al*., 2010).

3. Receptor-mediated adhesion:

Certain polymers bind to specific receptor sites on the cell surfaces, thereby enhancing the gastric retention of dosage forms.

Various investigators have proposed different mucin-polymer interactions, such as:

- ✶ Wetting and swelling of the polymer to permit intimate contact with the biological tissue.
- ✶ Interpenetration of bio adhesive polymer chains and entanglement of polymer and mucin chains.
- ✶ Formation of weak chemical bonds.

- ✶ Sufficient polymer mobility to allow spreading.
- ✶ Water transport followed by mucosal dehydration.

The bioadhesive coated system when comes in contact with the mucus layer, various non-specific (Vander Waals, hydrogen bonding and/or hydrophobic interactions) or specific interactions occurs between the complimentary structures and these interactions last only until the turnover process of mucin and the drug delivery system should release its drug contents during this limited adhesion time, in order for a bio adhesive system to be successful (Anand S. Surana *et al*., 2010).

5. Magnetic Systems

This approach to enhance the gastric retention time (GRT) is based on the simple principle that the dosage form contains a small internal magnet, and a magnet placed on the abdomen over the position of the stomach. Although magnetic system seems to work, the external magnet must be positioned with a degree of precision that might compromise patient compliance (Anand S. Surana *et al*., 2010; Sunil Kumar et al., 2012).

6. Super porous hydrogel systems

These swellable systems differ sufficiently from the conventional types to warrant separate classification. In this approach to improve gastric retention time (GRT) super porous hydrogels of average pore size >100 micro meter, swell to equilibrium size within a minute due to rapid water uptake by capillary wetting through numerous interconnected open pores . They swell to a large size (swelling ratio: 100 or more) and are intended to have sufficient mechanical strength to withstand pressure by gastric contraction. This is advised by co-formulation of hydrophilic particulate material (Sunil Kumar *et al*., 2012).

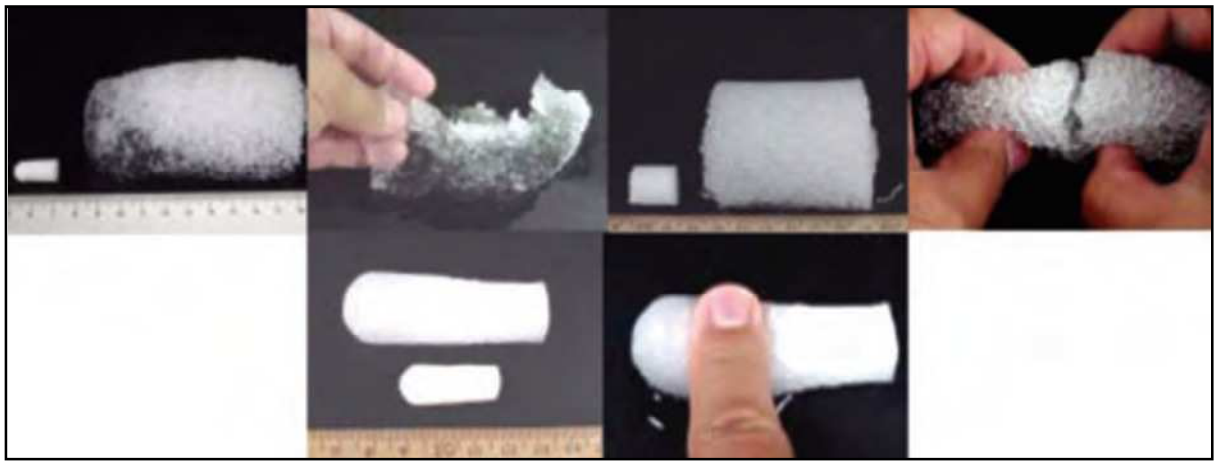


Figure 12: Typical swelling and mechanical properties of the SPH generations.

7. Raft-forming systems:

These systems, contain gel-forming solution (e.g. sodium alginate solution containing carbonates or bicarbonates), which on contact with the gastric contents, swells and forms a viscous cohesive gel containing entrapped CO_2 bubbles, releases drug slowly in stomach by forming the raft layer on the top of gastric fluid. These formulations contain antacids such as calcium carbonate or aluminium hydroxide to reduce gastric acidity (Neha Narang *et al*., 2011; Shah S.H *et al*., 2009).

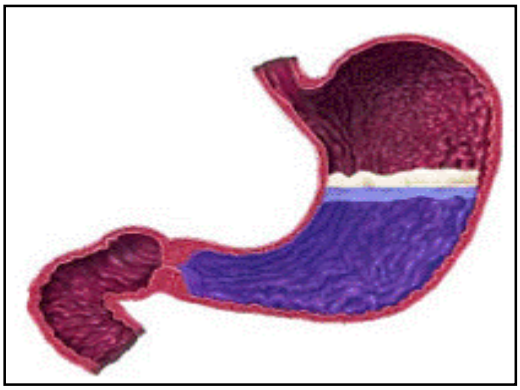


Figure 13: Schematic illustration of the barrier formed by a raft-forming system

CHAPTER III

FLOATING DRUG DELIVERY SYSTEM-REVIEW

The concept of FDDS was first described in the literature as early as 1968, when Davis (1968) disclosed a method to overcome the difficulty experienced by some persons of gagging or choking after swallowing medicinal pills. The author suggested that such difficulty could be overcome by providing pill having a density of less than 1.0g/cm^3, so that pill will float on water surface. Since then several approaches have been used to develop an ideal floating drug delivery system.

MECHANISM OF FLOATING DRUG DELIVERY SYSTEM

Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents (Figure 1), the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration (Praveen Nasa *et al*., 2010).

However, besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force (F) is also required to keep the dosage form reliably buoyant on the surface of the meal. The floating force kinetics is measured using a novel apparatus by determining the resultant weight (RW). The RW apparatus operates by measuring continuously the force equivalent to F (as a function of time) that is required to maintain the submerged object.

The object floats better if RW is on the higher positive side. This apparatus helps in optimising FDDS with respect to stability and durability of floating forces produced in order to prevent the drawbacks of unforeseeable intragastric buoyancy capability variations (Shah *et al*., 2009).

RW or F = F buoyancy - F gravity

= (Df - Ds) gV,

Where,

- ✶ RW = total vertical force,
- ✶ Df = fluid density,
- ✶ Ds = object density,
- ✶ V = volume and
- ✶ g = acceleration due to gravity.

In case of gas generating systems, carbon dioxide is released, causing the beads to float in the stomach. And in case of non-effervescent systems, the air trapped by the swollen polymer confers buoyancy to these dosage forms.

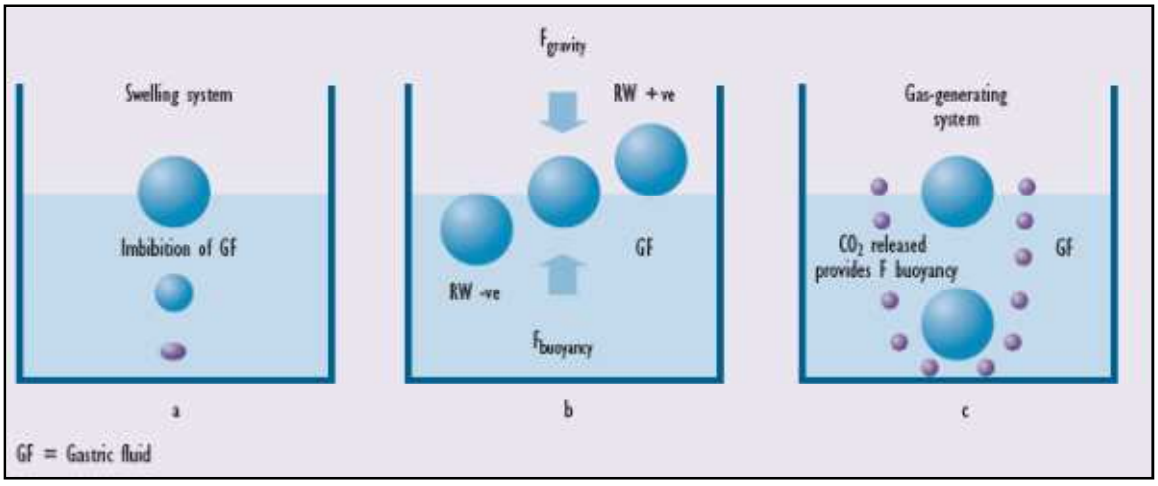


Figure 1: Mechanism of Floating systems

CLASSFICATION

Based on the mechanism of buoyancy, two different technologies have been used in development of floating drug delivery systems (Praveen Nasa *et al*., 2010). These include:

a) Non- Effervescent system.

b) Effervescent system.

NON-EFFERVESCENT SYSTEM

The Non-effervescent FDDS is based on mechanism of swelling of polymer or bioadhesion to mucosal layer in GI tract. The most commonly used excipients in noneffervescent. FDDS are gel forming or highly swellable cellulose type hydrocolloids, hydrophilic gums, polysaccharides and matrix forming materials such as polycarbonate, polyacrylate, polymethacrylate, polystyrene as well as bioadhesive polymers such as chitosan and carbopol (Amit Kumar Nayak *et al.,* 2010).

The various types of this system are as

1. Single layer floating tablets.
2. Bilayer floating tablets.
3. Alginate beads.
4. Hollow microspheres.

Single layer floating tablets

They are formulated by intimate mixing of drug with a gel-forming hydrocolloid, which swells in contact with gastric fluid and maintains bulk density of less than unity.

They are formulated by intimate mixing of drug with low-density enteric materials such as HPMC (Vinod K.R *et al*., 2010).

Bilayer floating tablets

A bilayer tablet contain **two layer** one immediate release layer which release initial dose from system while the another sustained release layer absorbs gastric fluid, forming an impermeable colloidal gel barrier on its surface, and maintain a bulk density of less than unity and thereby it remains buoyant in the stomach (Vinod K.R *et al*., 2010).

Alginate beads

Multi-unit floating dosage forms were developed from freeze dried calcium alginate. Spherical beads of approximately 2.5 mm diameter can be prepared by dropping sodium alginate solution into aqueous solution of calcium chloride, causing precipitation of calcium alginate leading to formation of porous system, which can maintain a floating force for over 12 hours. When compared with solid beads, which gave a short residence time of 1 hour, and these floating beads gave a prolonged residence time of more than 5.5 hours (Shah S.H *et al*., 2009; Vinod K.R *et al*., 2010).

Figure 2: Alginate beads

Hollow microspheres

Hollow microspheres (microballons), loaded with drug in their outer polymer shells were prepared by a novel emulsion-solvent diffusion method (Figure 3). The

ethanol: dichloromethane solution of the drug and an enteric acrylic polymer was poured into an agitated aqueous solution of PVA that was thermally controlled at 40^0C. The gas phase generated in dispersed polymer droplet by evaporation of dichloromethane formed an internal cavity in **microsphere of polymer with drug.** The microballons floated continuously over the surface of acidic dissolution media containing surfactant for more than 12 hours *in vitro* (Vinod K.R *et al*., 2010).

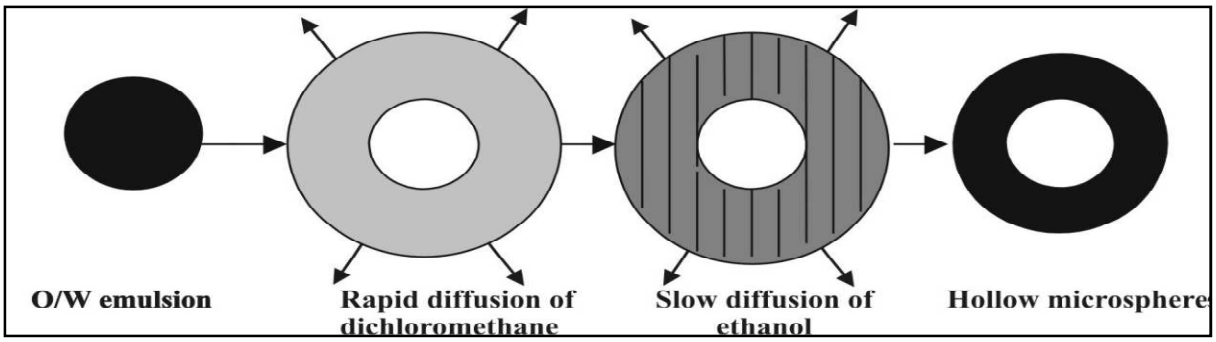


Figure 3: Formulation of floating hollow microsphere or microballoon

EFFERVESCENT SYSTEM

A drug delivery system can be made to float in the stomach by incorporating a floating chamber, which may be filled with vacuum, air or inert gas. The gas in floating chamber can be introduced either by volatilization of an organic solvent or by effervescent reaction between organic acids and bicarbonate salts (Shayeda *et al.,* 2009).

These effervescent systems further classified into two types:

1) Volatile liquid or vacuum containing systems.

2) Gas generating systems.

Volatile liquid or vacuum containing systems

(a) Intragastric floating gastrointestinal drug delivery system

This system floats in the stomach because of floatation chamber, which is vacuum or filled with a harmless gas or air, while the drug reservoir is encapsulated by a microporous compartment (Vinod K.R *et al*., 2010).

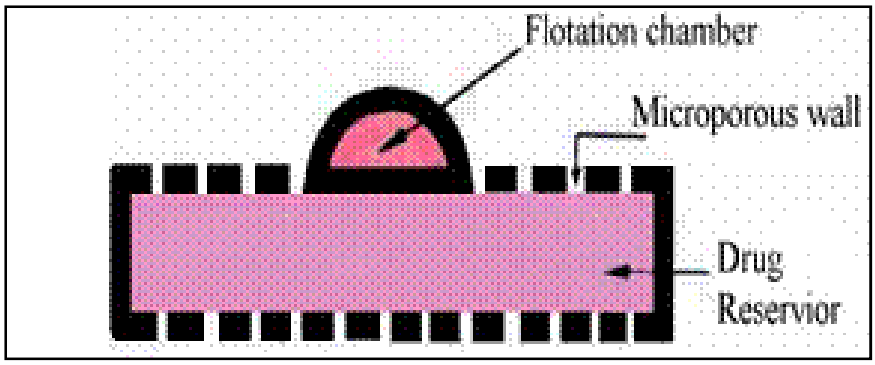


Figure 4: Intragastric floating gastrointestinal drug delivery device

(b) Inflatable gastrointestinal delivery systems

These systems are incorporated with an inflatable chamber, which contains liquid ether that gasifies at body temperature to inflate the chamber in the stomach. These systems are fabricated by loading the inflatable chamber with a drug reservoir, which can be a drug, impregnated polymeric matrix, then encapsulated in a gelatin capsule, (Figure 5). After oral administration, the capsule dissolves to release the drug reservoir together with the inflatable chamber. The inflatable chamber automatically inflates and retains the drug reservoir compartment in the stomach. The drug is released continuously from the reservoir into gastric fluid (Vinod K.R *et al*., 2010; Sunil Kumar *et al.,* 2012).

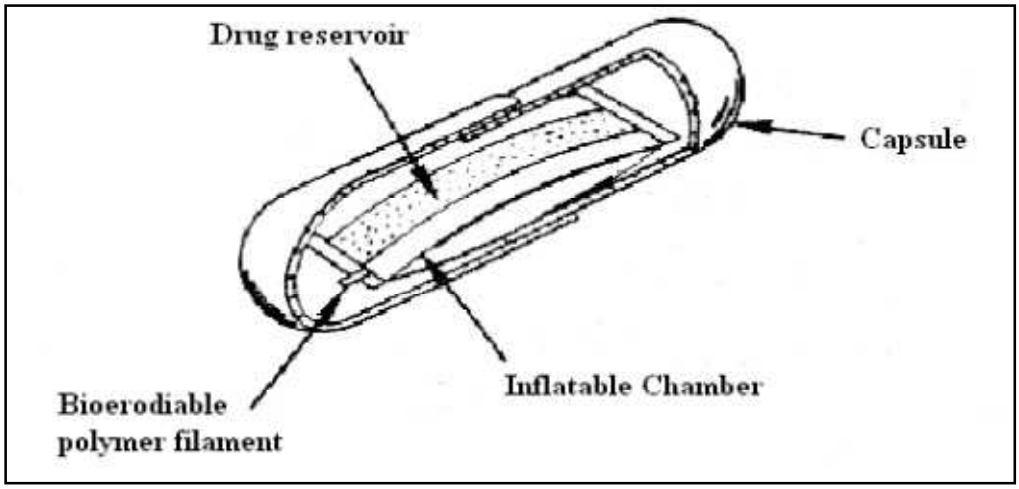
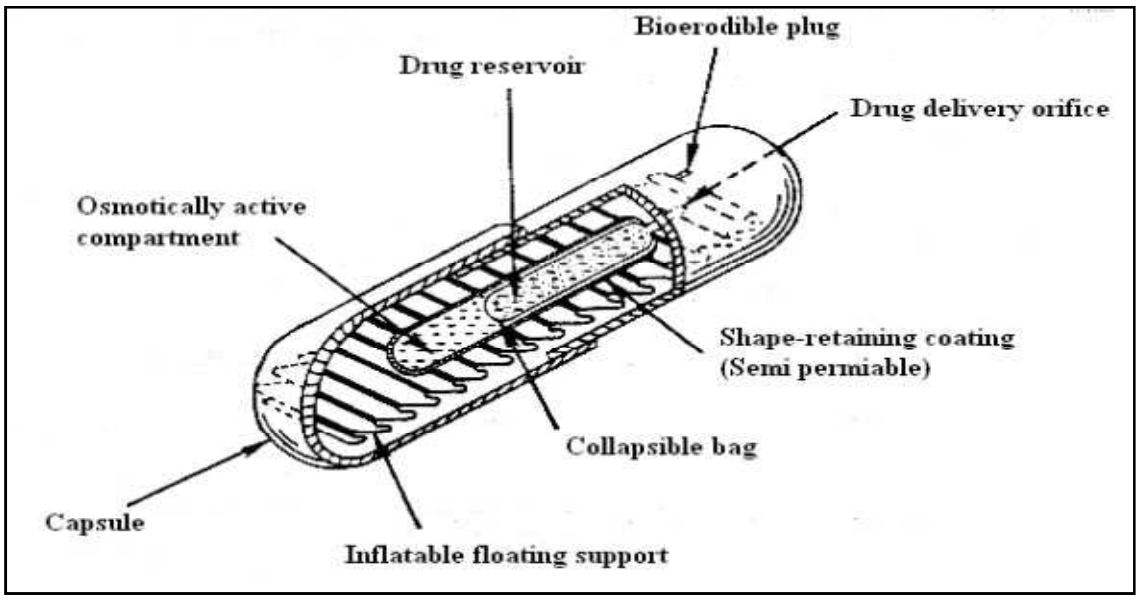


Figure 5: Inflatable gastrointestinal delivery system

(c) Intragastric osmotically controlled drug delivery system

This system is comprised of an osmotic pressure controlled drug delivery device and an inflatable floating support in a biodegradable capsule, (Figure 6). On contact with the gastric contents in the stomach, the capsule disintegrates quickly to release the intragastirc osmotically controlled drug delivery device. The inflatable support inside forms a hollow polymeric bag which contains a liquid that gasifies at body temperature to inflate the bag and it is deformable. The osmotic pressure controlled drug delivery device consists of two components, osmotically active compartment and a drug reservoir compartment. The drug reservoir compartment is enclosed by a pressure responsive collapsible bag, which is impermeable to liquid and vapour and has a drug delivery orifice. The osmotically active compartment contains an osmotically active salt and is enclosed within a semi-permeable housing. In the stomach, the osmotically active salt present in the osmotically active compartment is dissolved by absorbing the water continuously present in the GI fluid through the semi-permeable membrane. An osmotic pressure is thus created which acts on the collapsible bag and in turn forces the drug reservoir compartment to reduce its volume and activate the drug reservoir compartment



to reduce its volume and activate the drug release of a drug solution formulation through the delivery orifice. The floating support is also made to contain a bioerodible plug that erodes after a predetermined time to deflate the support. The deflated drug delivery system is then emptied from the stomach (Amit Kumar *et al*., 2011; Vinod K.R *et al*., 2010).

Figure 6: Intragastric osmotically controlled drug delivery system

GAS GENERATING SYSTEM

These buoyant delivery systems utilize effervescent reactions between carbonate/bicarbonate salts and citric/tartaric acid to liberate CO_2, which gets entrapped in the gellified hydrocolloid layer of the systems thus decreasing its specific gravity and making it to float over chyme (Sunil Kumar et al., 2012).

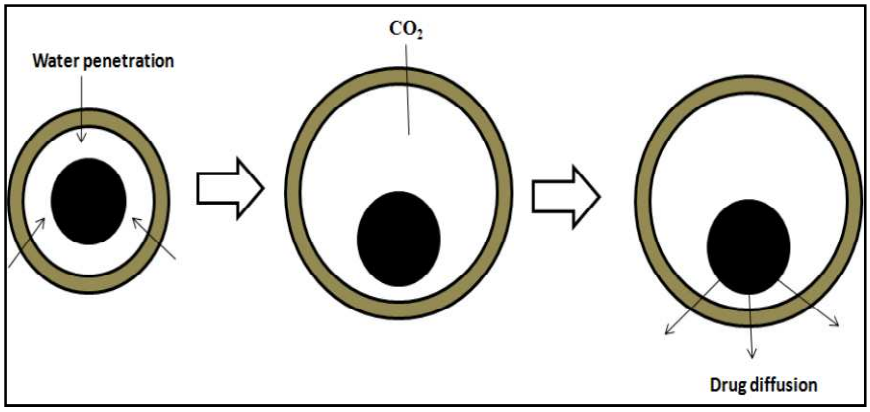


Figure 7: Drug release from effervescent (gas generating) systems

A) Tablets:

1. Intragastric single layer floating tablets or Hydrodynamically Balanced System (HBS)

These formulations have bulk density lower than gastric fluids and thus float in the stomach that increases the gastric emptying rate for a prolonged period, (Figure 8). These are formulated by intimately mixing the gas (CO_2) generating agents and the drug within the matrix tablet. The drug is released slowly at a desired rate from the floating system and the residual system is emptied from the stomach after the complete release of the drug. This leads to an increase in the gastric residence time (GRT) and a better control over fluctuations in plasma drug concentration (Vinod K.R *et al*., 2010; Sunil Kumar *et al*., 2012).

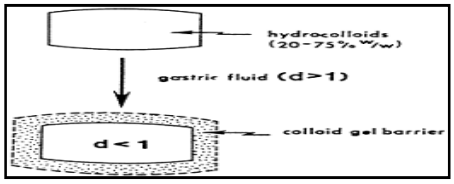


Figure 8: Intragastric single layer floating tablet

2. Intragastric bilayer floating tablets

These are also compressed tablets, containing two layers (Figure 9):

- ✶ Immediate release layer
- ✶ Sustained release layer.

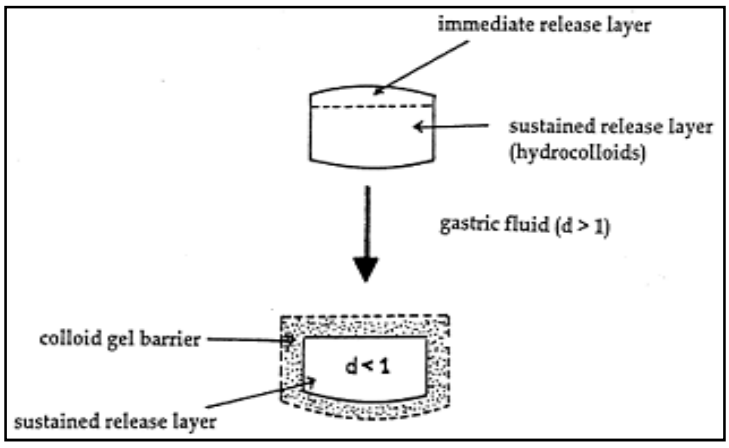


Figure 9: Intragastric bilayer floating tablet

B) Floating capsules

These floating capsules are formulated by filling with a mixture of sodium alginate and sodium bicarbonate. The systems float as a result of the generation of CO_2 that was trapped in the hydrating gel network on exposure to an acidic environment (Vinod K.R *et al*., 2010).

C) Multiple unit type floating pills

These multiple unit type floating pills are sustained release pills, known as 'seeds', which are surrounded by two layers (Figure 10). The outer layer is of swellable membrane layer while the inner layer consists of effervescent agents. This system sinks at once and then it forms swollen pills like balloons which float as they have lower density,

when it is immersed in the dissolution medium at body temperature. The lower density is due to generation and entrapment of CO_2 within the system (Amit Kumar *et al*., 2011; Vinod K.R *et al*., 2010).

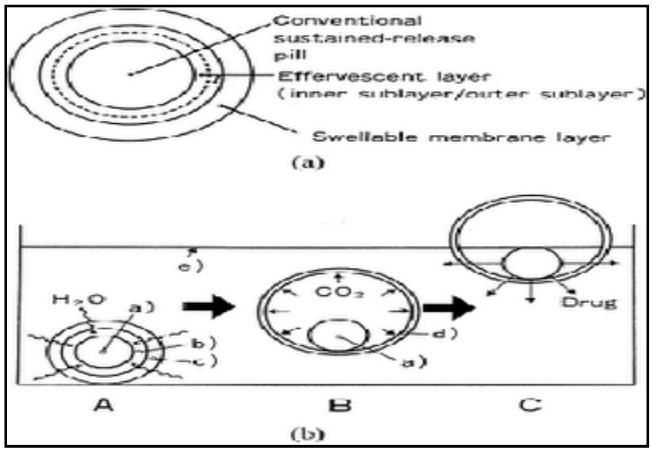


Figure: 10 (a) A multiple-unit oral floating dosage system. (b) Stages of floating mechanism: (A) penetration of water; (B) generation of CO_2 and floating; (C) dissolution of drug. Key: (a) conventional SR pills; (b) effervescent layer; (c) swellable layer; (d) expanded swellable membrane layer; (e) surface of water in the beaker (37^0C).

D) Floating system with Ion-Exchange resins

Floating system using bicarbonate loaded ion exchange resin was made by mixing the beads with 1M sodium bicarbonate solution, and then the semi-permeable membrane is used to surround the loaded beads to avoid sudden loss of CO_2. On contact with gastric contents an exchange of bicarbonate and chloride ions takes place that results in generation of CO_2 that carries beads towards the top of gastric contents and producing a floating layer of resin beads (Amit Kumar *et al*., 2011).

Advantages of Floating drug delivery system

1. The FDDS are advantageous for drugs absorbed through the stomach (e.g. ferrous salts) and for drugs meant for local action in the stomach and treatment of peptic ulcer disease (e.g. Antacids).

2. Acidic substances like aspirin cause irritation on the stomach wall when come in contact with it. Hence FDDS may be useful for the administration of aspirin and other similar drugs.

3. Administration of prolongs release floating dosage forms, tablet or capsules, will result in dissolution of the drug in the gastric fluid. They dissolve in the gastric fluid would be available for absorption in the small intestine after emptying of the stomach contents.

4. Drug will be fully absorbed from floating dosage forms if it remains in the solution form even at the alkaline pH of the intestine (Natasha Sharma *et al*., 2011)

5. FODDS provides advantages such as the delivery of drugs with narrow absorption windows in the small intestinal region (Vaishali Sharma *et al.,* 2011)

Disadvantages of Floating drug delivery system

1. These systems require a high level of fluid in the stomach for drug delivery to float and work efficiently coat, water.

2. Drugs that are significantly absorbed through out gastrointestinal tract, which undergo significant first pass metabolism, are only desirable candidate (Natasha Sharma *et al*., 2011)

3. Drugs that may irritate the stomach lining or are unstable in its acidic environment should not be formulated in gastro retentive systems (Vaishali Sharma *et al.,* 2011)

MARKETED PRODUCTS OF FDDS (Natasha Sharma et al., 2011; Shweta Arora *et al*., 2005)

S.NO	BRAND NAME	DRUG (DOSE)	COMPANY	REMARKS
1.	Modapar®	Levodopa (100mg) Benserazide (25mg)	Roche Products, USA.	Floating CR capsule
2.	Valrelease®	Diazepam (15mg)	Hoffmann-LaRoche USA	Floating capsule
3.	Liquid gavison®	Al hydrodxide (95mg), Mg carbonate (358 mg)	Glaxo Smith Kline, India	Effervescent floating liquid alginate preparation
4.	Topalkan®	Al-Mg antacid	Pierre Fabre Drug, France	Floating liquid alginate preparation
5.	Conviron®	Ferrous sulphate	Ranbaxy, India	Colloidal gel forming FDDS
6.	Cifran OD®	Ciprofloxacin (1 gm)	Ranbaxy, India	Gas-generating floating tablet
7.	Cytotec®	Misoprostal (100 mcg/200 mcg)	Pharmacia, USA	Bilayer floating capsule
8.	Oflin OD®	Ofloxacin (400 mg)	Ranbaxy, India	Gas generating floating tablet

POLYMERS AND OTHER INGREDIENTS USED IN THE FORMULATION OF FLOATING DRUG DELIVERY SYSTEM

Category	Materials
Polymers	HPMC K4 M, Calcium alginate, Eudragit S100, Eudragit RL, Propylene foam, Eudragit RS, ethyl cellulose, polymethyl meth acrylate, Methocel K4M, Polyethylene oxide, β Cyclodextrin, HPMC 4000, HPMC 100, CMC, Polyethylene glycol, polycarbonate, PVA, Polycarbonate, Sodium alginate, HPC-L, CP 934P, HPC, Eudragit S, HPMC, Metolose S.M. 100, PVP, HPC-H, HPC-M, HPMC K15, Polyox, HPMC K4, Acrylic polymer, E4 M and Carbopol
Inert fatty materials (5%-75%)	Edible, inert fatty materials having a specific gravity of less than one can be used to decrease the hydrophilic property of formulation and hence increase buoyancy. E.g. Beeswax, fatty acids, long chain fatty alcohols, Gelucires® 39/01 and 43/01.
Effervescent agents	Sodium bicarbonate, citric acid, tartaric acid, Di-SGC (Di-Sodium Glycine Carbonate), CG (Citroglycine)
Release rate accelerants (5%-60%)	lactose, mannitol
Release rate retardants (5%-60%)	Dicalcium phosphate, talc, magnesium stearate
Buoyancy increasing agents (upto80%)	Ethyl cellulose
Low density material	Polypropylene foam powder (Accurel MP 1000®)

EVALUATION OF FLOATING DRUG DELIVERY SYSTEMS

(1) PRELIMINARY EVALUATION:

a) Buoyancy Lag Time

- ✶ It is determined in order to assess the time taken by the dosage form to float on the top of the dissolution medium, after it is placed in the medium. These parameters can be measured as a part of the dissolution test.

b) Floating Time

- ✶ Test for buoyancy is usually performed in SGF-Simulated Gastric Fluid maintained at 37^0C. The time for which the dosage form continuously floats on the dissolution media is termed as floating time.

(2) *IN VITRO* DISSOLUTION TESTS

- ✶ *In vitro* dissolution test is generally done by using USP apparatus with paddle and GRDDS is placed normally as for other conventional tablets. But sometimes as the vessel is large and paddles are at bottom, there is much lesser paddle force acts on floating dosage form which generally floats on surface. As floating dosage form not rotates may not give proper result and also not reproducible results. Similar problem occur with swellable dosage form, as they are hydrogel may stick to surface of vessel or paddle and gives irreproducible results. In order to prevent such problems, various types of modification in dissolution assembly made are as follows.
- ✶ To prevent sticking at vessel or paddle and to improve movement of dosage form, method suggested is to keep paddle at surface and not too deep inside dissolution medium.

- ✶ Floating unit can be made fully submerged, by attaching some small, loose, non reacting material, such as few turns of wire helix, around dosage form. However this method can inhibit three dimensional swelling of some dosage forms and also affects drug release.
- ✶ Other modification is to make floating unit fully submerged under ring or mesh assembly and paddle is just over ring that gives better force for movement of unit.
- ✶ Other method suggests placing dosage form between 2 ring/meshes.
- ✶ In previous methods unit have very small area, which can inhibit 3D swelling of swellable units, another method suggest the change in dissolution vessel that is indented at some above place from bottom and mesh is place on indented protrusions, this gives more area for dosage form.
- ✶ Inspite of the various modifications done to get the reproducible results, none of them showed co-relation with the *in vivo* conditions. So a novel dissolution test apparatus with modification of Rossett-Rice test Apparatus was proposed.

(3) *IN VIVO* EVALUATION

a) Radiology

- ✶ X-ray is widely used for examination of internal body systems. Barium Sulphate is widely used Radio Opaque Marker. So, BaSO4 is incorporated inside dosage form and X-ray images are taken at various intervals to view GR.

b) Scintigraphy

- ✶ Similar to X-ray, emitting materials are incorporated into dosage form and then images are taken by scintigraphy. Widely used emitting material is 99Tc.

c) Gastroscopy

- ✶ Gastroscopy is per oral endoscopy used with fibre optics or video systems. Gastroscopy is used to inspect visually the effect of prolongation in stomach. It can also give the detailed evaluation of GRDDS.

d) Magnetic Marker Monitoring

- ✶ In this technique, dosage form is magnetically marked with incorporating iron powder inside, and images can be taken by very sensitive bio-magnetic measurement equipment. Advantage of this method is that it is radiation less and so not hazardous.

e) Ultrasonography

- ✶ Used sometimes, not used generally because it is not traceable at intestine **(**Shweta Arora *et al*., 2005; Gopalakrishnan S *et al.,* 2011).

APPLICATIONS OF FLOATING DRUG DELIVERY SYSTEM

Sustained drug delivery:

Hydrodynamically Balanced System (HBS) type are dosage forms which have bulk density less than one, relatively large in size and did not easily pass through pylorus, releases the drug over a prolonged period of time by retaining in the stomach for several hours and by increasing the gastric residence time (Kwon H. Kim *et al*., 2000).

Site specific drug delivery:

Floating drug delivery systems are particularly useful for drugs having specific absorption from stomach or proximal part of the small intestine e.g. riboflavin,

furosemide etc. The absorption of captopril has been found to be site specific, stomach being the major site followed by duodenum (Amit Kumar *et al*., 2011).

Absorption enhancement:

Drugs that have poor bioavailability, because of their absorption is restricted to upper GIT are potential candidates to be formulated as floating drug delivery systems, thereby improving their absolute bioavailability.

Minimized adverse activity at the colon

Retention of the drug at the stomach (HBS system), minimizes the amount of drug that reaches the colon, that prevents the undesirable activities of the drug in colon. This Pharmacodynamic aspect provides the rationale for GRDF formulation for betalactam antibiotics that are absorbed only from the small intestine, and whose presence in the colon leads to the development of microorganism's resistance.

Reduction in plasma fluctuations:

Patients with advanced Parkinson's disease, experienced pronounced fluctuations in symptoms while treatment with standard L-dopa. A HBS dosage form provided a better control of motor fluctuations although its bioavailability was reduced by 50-60% of the standard formulation.

Peptic ulcer treatment:

H. Pylori, causative bacterium for peptic ulcers and chronic gastritis. Patients require high concentration of drug, to be maintained at the site of infection that is within the gastric mucosa. The floating dosage form due to its floating ability was retained in

stomach and maintained high concentration of drug in the stomach. A sustained liquid preparation of Ampicillin, using sodium alginate was developed that spreads out and adheres to gastric mucosal surfaces and releases the drug continuously.

Suitable for poorly absorbed drugs.

Floating drug delivery systems are particularly useful for drugs which are poorly soluble or unstable in intestinal fluids and acid stable drugs and for those which undergo abrupt changes in their pH-dependent solubility due to pathophysiological conditions of GIT, food and age, e.g. floating system for furosemide lead to potential treatment of Parkinson's disease. Approximate 30% drug was absorbed after oral administration (Shweta Arora *et al*., 2005).

CHAPTER IV

LITERATURE REVIEW

Pramad Patil *et al*., 2011, developed the floating tablets of ofloxacin which were designed to prolong the gastric residence time after oral administration. It was found that increase in HPMC K100M concentration will decrease floating lag time and increases floating duration but decrease drug release.

Mahajan P *et al*., 2011, developed the antihypertensive sustained release matrix tablets of valsartan using HPMC alone and in combination with ethyl cellulose as the matrix material in different proportion by wet granulation method. It was concluded that dissolution study indicated the formulation prepared by low viscosity grade HPMC showed maximum drug release upto 8 hrs and high viscosity grade HPMC and EC showed upto 12 hrs.

Rajhans S *et al*., 2011, reported that swellable gastro retentive drug delivery system was developed using combination of polyethylene oxide and HPMC K100LV by wet granulation process. Based on the release kinetics it can be concluded that this combination of polyox WSR 303 and HPMC K100LV is particularly suitable as gastro retentive drug delivery system of valsartan as extended release drug delivery system.

Sathiyaraj S *et al.,* 2011, formulate lornoxicam floating tablets proved that a hydrophobic drug can be designed as modified release dosage form with desired qualities, using hydrophilic polymer HPMC K15M and calcium carbonate as a buoyancy initiator. Additionally, ease of manufacturing process by direct compression implies that it ensures the capability of commercial utility by large scale production with satisfactory industrial feasibility.

Jeetendra Singh Negi *et al.,* 2011, developed the gastro retentive floating bilayer tablets of atenolol by using natural excipient psyllium husk was utilized in combination with HPMC K4M in floating layer of bilayer tablets. In the absence of psyllium husk the tablets were not having constant floating behavior for 10 hours duration with inclusion of psyllium husk the constant floating behavior was successfully achieved.

Vandana Jugran *et al*., 2011, formulate non-effervescent floating matrix based on euryale ferox seeds has been incorporated into HPMC K4M. The buoyancy is provided by high air content due to natural porous network of EFSP. This reduction in drug release is due to increase in drug diffusion length in viscous gel layer.

Krunal Patel M *et al.,* 2011, prepared floating tablets of mebendazole by using chitosan & HPMC, sodium bicarbonate. The specific study was carried out to formulate such a dosage form that can neutralize the acidity locally in the stomach. The granulation was formed by fluidized bed processor in which top spray technique was adopted for forming the granules.

Netta Narang *et al*., 2011, had done a project in gastro retentive floating drug delivery system using a gas-forming agent like sodium bicarbonate & polymer like HPMC. The anti-retroviral therapy of stavudine, the drug has to administer for long period of time and due to this more drug will be accumulated in the body which ultimately increases the side effects and is formulated as effervescent floating drug delivery system.

Jeetendra Singh Negi *et al.,* 2011, investigate the effect of bioadhesion on the initial *in vitro* buoyancy behavior of effervescent matrix tablets of ciprofloxacin Hcl prepared by direct compression method using HPMC K4M and carbopol 971P, sodium bicarbonate.

The drug release was associated with both swelling and erosion of polymeric chains and sustained for 12 hours.

Shailesh Prajapati *et al.,* 2011, prepared floating matrix tablet of domperidone by simplex lattice design. It was concluded that the content of PEO had a dominating role as drug release controlling factor, but using suitable concentration of sodium bicarbonate, one can tailor the desired drug release from hydrophilic matrixes for the development of floating tablets.

Muniyandy Saravanan *et al.,* 2011, developed ranitidine hydrochloride loaded floating microspheres by novel solvent evaporation matrix erosion method using ethyl cellulose and polyethylene glycol blend. The microspheres sustained the drug release over a period of 4-6h. The above results revealed the possibility of development of floating drug delivery system using EC/PEG polymer blend for sustained and local delivery in the stomach.

Dorozynksi *et al.*, 2011, investigated the effects of carrageenam, and hydroxypropylmethylcellulose on the properties of hydrodynamically balanced systems containing L-dopa as a model drug. The effect produced by varying the polymer blend's composition on release of the L-dopa was also studied. The matrices containing mixtures of carrageenam and HPMC, the linear increase in the releasing rate constant, with the carrageenam content in the matrix was observed.

Meka Venkata Srikanth *et al.,* 2011, prepared floating tablet of propranolol Hcl by statistical design and to investigate the effect of formulation variables on drug release and the buoyancy properties of the delivery system. The present study clearly indicates the

applicability of statistical optimization techniques to predict the composition of a formulation that gives optimum product parameters.

Ming-Thau Sheu *et al.*, 2010, developed an optimal gastro retentive drug delivery system for administering losartan. Additionally, the influence of optimized GRDDS on the bioavailability of losartan and the formation extent of active metabolite E3 174 by CYP2 C9 polymorphism was investigated. The lower bioavailability of losartan in the CYP2C9*1/*1 subjects than CYP2C9*1/*3 subjects was found and could be due to the variety of enzymatic activity.

Sharad N. Shinde *et al*., 2010, floating matrix tablets of salbutamol sulphate were prepared by wet granulation method by using HPMC as a release retardant material and sodium bicarbonate, citric acid was incorporated as a gas-generating agent. The addition of release rate enhancer and release rate retardant showed excellent balance in drug release rate and floating characteristics.

Sivabalan M *et al*., 2010, formulated and evaluates hydrodynamically balanced controlled drug release of glipizide with enhanced bioavailability and reduced dosing frequency. The optimized formulation G8 exhibited responses that were comparable with that of the predicted values of the design in optimization technique.

Ritesh Kumar *et al*., 2010, formulate floating matrix tablets of metformin hydrochloride were developed and evaluated for increase bioavailability by increasing gastric residence time and sustained release of drug on the upper part of GIT thereby diminishing side effects and enhanced patient compliance.

Mukhopadhyay S *et al*., 2010, present study it was concluded that floating bioadhesive tablets of ciprofloxacin hydrochloride can increase the gastric residence time as well as bioavailability and thus better patient compliance can be achieved.

Wamorkar V.V *et al*., 2010, present study on developing the floating drug delivery was carried out in order to control release of metoclopramide hydrochloride using combination of hydrophilic and hydrophobic polymers. Thus results of the current study clearly indicate, a promising potential of the metoclopramide hydrochloride floating system as an alternative to the conventional dosage form.

Chander Shekar B *et al*., 2010, prepared a gastro retentive drug delivery system of ketoconazole by direct compression method by using HPMC, EC and effervescent sodium bicarbonate. It was concluded that *in vitro* drug release profiles obtained for tablets made with combinations of HPMC K4M, HPMC K15M and ethyl cellulose showed lesser floating lag time and a prolonged floating duration which was a controlled release characteristic.

Arunachalam A *et al*., 2010, present study is to develop a floatable drug delivery system of levofloxacin hemihydrate for sustained drug delivery and gastric retentive property with special emphasis on optimization of formulations for floating matrix tablets. To improve the oral bioavailability of the drug and to achieve extended retention in stomach this may result in prolonged absorption.

Londhe S *et al.,* 2010, purpose of the research work was development and evaluation bi-layer floating tablets for verapamil hydrochloride. The results of this study based on *in vitro* characterization biphasic drug releases from bilayer floating tablets which float

more than 12 hours in dissolution medium and *in vivo* study showed that tablet was float more than 7 hours in gastric region.

Ramesh C *et al*., 2010, gastro floating tablets of cinnarzine were fabricated by direct compression method by using four viscosity grades of HPMC, sodium alginate and gas forming agent. It was concluded that the greater bioavailability studies in rabbits of HP1 was due to its longer retention in the gastric environment of the test animal, 24 hours sustained release formulation.

Liandong Hu *et al*., 2010, developed dextromethorphan hydrobromide sustained release tablets using floating technique to prolong the gastric residence time and compared their pharmacokinetic behavior with conventional sustained release tablets. The results showed the floating tablets are a feasible approach for the sustained release preparation of drugs, which have limited absorption sites in the stomach.

Ajay Bagherwal *et al*., 2010, present study, it was aimed to formulate floating tablet of ciprofloxacin Hcl with HPMC and Carbomer in different proportion by direct compression techniques using polymers, lactose, magnesium stearate, talc with sodium bicarbonate. The drug release from the system was found to be concentration independent and diffusion mediated.

Debajyoti Ray *et al*., 2010, developed floating drug delivery system of tramadol hydrochloride was prepared using different grades of HPMC and sodium bicarbonate as source for carbon dioxide which helps tablets to float. It was concluded from the results, the release studies of the formulations F5 was found to have better drug release profile than other formulations.

Shreeraj H. Shah *et al*., 2010, purpose of the present study was to develop an optimized gastric floating drug delivery system containing gatifloxacin with combination of polymers using box-behnken experimental design. When they used in combination for developing GFDDS, high to moderate amount of compritol ATO 888, low to moderate amount of poloxamer 188 and low to high amount of chitosan is to be used to achieve the desired floating lag time.

Deshbhratar R M *et al*., 2010, formulated gastro retentive floating tablets of carbamazepine by using HPMC of different viscosity grades and ethyl cellulose were used in formulating the gastric floating drug delivery system. It was concluded that the higher viscosity seems to inhibit the initial burst effect of carbamazepine release from the GFDDS; it does not seem to affect the carbamazepine release rate. Ethyl cellulose however is found to comprise the release properties of drug candidate from GFDDS.

Yasir M *et al*., 2010, developed one daily SR floating matrix tablet for theophylline using psyllium husk as release controlling polymer and to compare the release pattern with synthetic polymer HPMC K100M. It can be concluded that psyllium husk can be a promising polymer for GRFDDS in combination with synthetic polymers (HPMC K15M), and enhanced the floating duration and help to maintain the dimensional stability at initial stage, which is necessary in case of once daily formulations.

Mohammad Asif *et al*., 2010, developed sustained release floatable tablet for fluvastatin sodium prepared from mixture of HPMC K4M and carbopol 934P using gas generating agent. The effervescent floating tablet showed more drug release than non-effervescent floating tablet. It was concluded that viscosity is a major factor affecting the release and floating properties of the GFDDS. On increasing the concentration of this hydrogel

polymer, decrease the release rate of drug. The higher viscosity seems to inhibit the initial burst effect of fluvastatin sodium release from GFDDS.

Ganesh Kumar Gudas *et al*., 2010, the present study was carried out to develop floating tablet of norfloxacin in order to enhance the absorption and bioavailability of the drug by increasing the gastric retention time in the stomach. The incorporation of sodium bicarbonate helps to improve floating properties by reacting with gastric fluid when dosage form comes in contact and produce carbon dioxide gas which entrapped inside the hydrophilic matrixes leads to increase in volume of dosage form resulting in lowering of density and dosage form starts to float.

Mahesh Molke *et al*., 2010, prepared a gastro retentive drug delivery system of verapamil Hcl employing solid dispersion technique with compritol 888 ATO by using different release enhancer like lactose, microcrystalline cellulose & HPMC K100 LV. The product was evaluated for buoyancy, drug content and *in vitro* dissolution test.

Baljit Singh *et al*., 2010, to synthesize gastroretentive floating drug delivery system by simultaneously ionotropic gelation of alginate and sterculia gum by using $cacl_2$ as cross linker. At the same time floating nature of beads can make the retention of drug delivery systems in the stomach for longer time and may improve the bioavailability and therapeutic efficacy of the drugs used for the diseases associated with the stomach.

Ganaprakash K *et al*., 2010, formulate floating tablets of famotidine was prepared with isolation chitosan by wet granulation technique. In the present study the floating tablets of famotidine showed better gastric cytoprotection when compared with conventional dosage form. This may be due to its extended duration of release and action.

Margret Chandira R *et al*., 2010, formulates floating tablets of itopride hydrochloride using an effervescent approach for GRDDS by direct compression method. The floating tablet formulations were evaluated for physical characterization, swelling index, assay, *in vitro* drug release, weight variation. The results indicated that gas powered floating tablets of itopride hydrochloride containing 125mg HPMC K100M, 40mg HPMC K15M, and 40mg of carbopol provides a better option for 24hours release action and improved bioavailability.

Lingaraj S. Danki *et al*., 2010, present study in the development of hydrodynamically systems of alfuzosin Hcl by direct compression method using HPMC. It was concluded that alfuzosin Hcl for increasing the bioavailability and reliability for hypertension and in benign prostatic hyperplasia to relieve symptoms of urinary obstruction by allowing a better control of fluctuations observed with conventional dosage forms.

Mandal S *et al*., 2010, designed and evaluation of gastro retentive sustained release tablets of tizanidine Hcl using HPMC K100 by direct compression method. The tablets were evaluated for Pharmacopeial and non-Pharmacopeial tests. *In vitro* release profiles of optimized formulations were found to be similar to that of commercial marketed product.

Jadhav Mayur N *et al*., 2010, prepare a gastro retentive drug delivery system of famotidine was prepared by employing polymers like guar gum and xanthan gum by effervescent techniques. It was also concluded that the formulations which contained combination of guar gum and xanthan gum was more effective in modifying the drug release pattern as compared to the formulations that contains individual polymer. The optimum formulation was found to be stable during the short term stability testing.

Mishra Manoj Kumar *et al*., 2010, gastro retentive floating tablet of ondansetron Hcl were formulated by using various low density polymers, which not only imparted buoyancy to the formulations but also reduced floating lag time to a great extent. It may be concluded from the present study that slow, controlled and complete drug release of ondansetron over a period of 12 hours was obtained from FT10.

Rajashree Masareddy *et al*., 2010, developed single and bilayer tablets of riboflavin were prepared by direct compression technique using HPMC K4M, carbopol and other excipients. Carbopol containing tablets were retained in stomach by mucoadhesion mechanism and HPMC containing tablets were retained in stomach by non-mucoadhesion mechanism. *In vitro* release results indicated that the drug release was more sustained in carbopol with lactose containing formulations.

Anilkumar J. Shinde *et al*., 2010, formulate an oral floating tablet of cephalexin using the hydrophilic polymer HPMC, gas generating agent sodium bicarbonate and citric acid by 3^2 factorial design. The results of factorial design indicated that high level of HPMC K100M and citric acid favors preparation of floating sustained release tablet of cephalexin.

Nagalakshmi S. *et al*., 2009, formulated and evaluated floating matrix tablets of Pioglitazone Hcl by non-effervescent and effervescent techniques. The best formulation was identified as that containing HPMC K100 M which exhibited good floating behavior and good controlled release properties.

Rishad R. Jivani *et al*., 2009, present investigation describes the design and development of self correcting monolithic gastro retentive system of baclofen tablets were prepared by direct compression method. It was concluded that gastro retentive tablet of baclofen can

be prepared via floating and bioadhesion mechanism to increase residence time of drug in stomach and thereby increase absorption.

Damodharan N *et al*., 2009, developed bilayer floating tablets of theophylline by wet granulation technique using HPMC, methylcellulose, sodium carboxy methyl cellulose and the tablets were evaluated. The formulated tablets employing a combination of HPMC and methylcellulose provide slow release of theophylline over a period of 9 hours and were found suitable for maintenance portion of bilayer floating tablets.

Ajit Kulkarni *et al*., 2009, study was performed to design bilayer regioselective floating tablets of atenolol and lovastatin. Bilayer floating tablets having different release profiles for different drugs can be formulated using HPMC K100M and xanthan gum (alone and in combination) to give controlled release of atenolol and sodium starch glycollate to give immediate release of lovastatin. Hence this dosage form should be further evaluated for delivery of two drugs form, a single dosage form which could improve patient compliance and give better disease management.

Aliasgar Shahiwala *et al*., 2009, statistical optimization of ranitidine Hcl floating pulsatile delivery system for chronotherapy of nocturnal acid breakthrough. The proposed mathematical model is found to be robust and accurate for optimization of time logged coating formulations for programmable pulsatile release of ranitidine hydrochloride, consistent with the demands of nocturnal acid breakthrough.

Monica RP Rao *et al.,* 2009, developed effervescent floating tablets of salbutamol sulphate by using HPMC and gas generating agent. Stearic acid provides an acidic environment to sodium bicarbonate, which reduces the BLT in the fed condition. All formulations had a desired floating time regardless of the viscosity grade of HPMC. The

mechanism of drug release was found to be of the anomalous type, which validates the reported behavior for the matrix tablets.

Pare A *et al*., 2008, developed effervescent floating tablets of amlodipine besylate by employing different grades of polymers and effervescent agents such as sodium bicarbonate and citric acid. From above the results, the effervescent floating tablet containing amlodipine besylate gave slow and complete drug release spread over 24 hours and compare with marketed product.

Arunkumar N *et al*., 2008, present study was aimed at developing an oral floating system for atrovastatin calcium with the use of a swellable polymer, release retardant and an alkalizing agent which proved to be an ideal formulation, as it released the drug in a controlled manner for prolonged period, the dose can be reduced and possible incomplete absorption of the drug can be avoided.

Leopoldo Villafuerte Robles *et al*., 2008, developed controlled release formulation of captopril from metolose SH 4000 SR/Sodium bicarbonate, varying the proportions of metolose and bicarbonate. The drug release constant decreases and the exponent indicative of the release mechanism increases with increasing polymer contents. Carbon dioxide bubbles obstruct the diffusion path and decrease the matrix coherence.

Manoj N. Gambhire *et al*., 2007, had done a project in effervescent based floating drug delivery of dilitiazem Hcl by using gel forming polymer. Combination of methocel K100M CR and compritol 888 ATO has resulted in minimal variation in drug release. The optimized formulation gives the best result in terms of the required lag time and floating duration of 24 hours, and drug release was in accordance with the USP

dissolution criteria for extended release capsule for dilitiazem and matched with marketed formulation.

Narendra C *et al*., 2006, optimization of bilayer floating tablet containing metoprolol tartrate by factorial designing in which polymer HPMC K4M did not significantly affect the floating design consists of 8 full factorial designs, dependent variables and independent variables were selected. The dosage form can control the release, avoid dose dumping, and extend the duration of action of a drug with prolonged floating time.

Ziyaur Rahman *et al*., 2006, developed a bilayer floating tablet of captopril using direct compression technology using various grades of HPMC. *In vitro* dissolution studies showed controlled release for 24 hours, followed by the Higuchi diffusion mechanism and *in vivo* studies indicated increased GRT. Thus, the results of the current study clearly indicate, a promising potential of the captopril floating system as an alternative to the conventional dosage form.

Atmaram P Pawar *et al.*, 2006, designed gastro retentive delivery system for bimodal release of cefuroxime axetil. Thus, bimodal drug release comprising of immediate release for quick onset of action followed by controlled release minimizing the concentration of unabsorbed drug entering colon was achieved.

Brijesh *et al.*, 2004, discusses the preparation of gastro retentive tablets of ranitidine hydrochloride by effervescent techniques. The addition of gel forming polymer HPMC K4M and gas generating sodium bicarbonate was essential to achieve *in vitro* buoyancy. A systematic study using a 3^2 factorial design revealed that the amount of citric acid and stearic acid had a significant effect on t_{50}, t_{80} and F2.

Sasa Baumgartner *et al.*, 2000, formulated floating matrix tablets pentoxyfilline by using HPMC K4M, avicel PH 101 and a gas generating agent. The release rate constant of this formulation was low enough prolonging drug delivery. This result is encouraging, because a longer gastric residence time and higher bioavailability of the drugs.

CHAPTER V

AIM AND OBJECTIVE OF THE WORK

- Cardiovascular diseases are one of the life threatening diseases in the world. Angina pectoris, hypertension and cardiac failure are the commonest diseases and require constant monitoring. Hypertension is progressive and complex disorders that are difficult to treat effectively in the long term. Antihypertensive drugs play a major role in the management of hypertension. There is a wide range of oral antihypertensive drugs, indicated for the treatment of hypertension which may be used monotherapy or in combination with others.

- Valsartan is a potent orally active non peptide tetrazole derivative and selectively inhibits (ACE Inhibitor) angiotensin II receptor type 1 which causes reduction in blood pressure and it's widely prescribed for treatment of hypertension. Since the drug is prefentially absorbed in the upper GIT (narrow absorption window), the drug displays oral bioavailability problems as given in conventional dosage forms.

- An conventional dosage forms can only partly satisfy therapeutic and biopharmaceutical needs, as it doesn't take into account the site specific absorption rates within the GIT, therefore there is a need for developing delivery system that release the drug at the right time, at the specific site and with the desired rate.

- To overcome these problems, different approaches have been proposed to retain dosage form in the stomach. One of the most feasible approach for achieving a prolonged and predictable drug delivery in the GIT is to control the Gastric Residence Time (GRT) (i.e. Gastro retentive dosage form). This dosage form can be retained in the stomach and assist in improving the oral sustained delivery of drugs that have an absorption window in a particular region of the GIT, thus ensuring optimal bioavailability. Gastro retention can be achieved via Intragastric floating drug delivery system, High density system, Swelling (or) Expandable system and Superporous hydrogels.

- The objective of the present study is to develop a floatable dosage forms of Valsartan are prepared by non-effervescent technique using two different polymers hydrophilic and hydrophobic polymers are designed to prolong the gastric residence time and to enhance the drug bioavailability. The main aim of the work is to evaluate the effect of both hydrophilic and hydrophobic polymer on *Invitro* drug release, Floating behavior, and In *vivo* x-ray studies.

CHAPTER VI
PLAN OF WORK

The plan of the work involves the following steps:

STEP-I

STANDARD CALIBRATION CURVE OF VALSARTAN

(a) Preparation of dissolution medium

(b) Determination of (Absorption Maximum) λ_{max} of Valsartan by UV spectrum

(c) Preparation of standard calibration curve for Valsartan

STEP-II

PREFORMULATION (COMPATABILITY) STUDIES

(a) Differential scanning calorimetric (DSC) studies

(b) Fourier Transform Infra Red Spectroscopic (FT-IR) studies

STEP-III

FORMULATION OF VALSARTAN FLOATING MATRIX TABLET

- ✶ Preparation of Floating matrix tablets of valsartan using different concentrations of hydrophilic and hydrophobic polymers (HPMCK100M, HPMCK15M, HPMC K4M, MC & EC) by using non effervescent technique.

STEP-IV

EVALUATION OF VALSARTAN FLOATING MATRIX TABLET

1. PRECOMPRESSIONAL EVALUATION OF POWDER BLEND:

(a) Angle of Repose

(b) Bulk Density

(c) Tapped Density

(d) Compressibility Index

(e) Hausner's Ratio

(f) Estimation of drug content for powder blend

2. POSTCOMPRESSIONAL EVALUATION OF VALSARTAN FLOATING TABLET:

(a) General appearance

(b) Hardness

(c) Thickness & Diameter

(d) Friability test

(e) Weight variation test

(f) Estimation of drug content for tablets

3. *IN VITRO* BUOYANCY STUDIES

4. SWELLING STUDIES

5. *IN VITRO* RELEASE STUDIES

6. *IN VITRO* DRUG RELEASE KINETICS STUDIES

STEP-V

SELECTION OF BEST FORMULATION

(A) Evaluation of best formulation

1. Comparison with marketed formulation

2. Assay by High performance liquid chromatography (HPLC) method.

3. Scanning Electron Microscopy (SEM)

4. *In vivo* x-ray studies

5. Stability studies

CHAPTER VII

MATERIALS AND EQUIPMENTS

MATERIALS:

S. NO	NAME	SUPPLIER OF MATERIAL
1.	Valsartan	Gift sample from Dr. Reddys Lab. Pvt. Ltd., Hyderabad, Ranbaxy, Gurgan & Tablets India, Chennai
2.	HPMC (different grades)	Gift samples from Shasun Pharma, Pondicherry & Dr. Reddys Lab. Pvt. Ltd., Hyderabad.
3.	Methyl Cellulose	Gift sample from Shasun Pharma, Pondicherry
4.	Ethyl cellulose	Gift sample from Dr. Reddys Laboratory, Hyderabad
5.	Lactose	Central Drug House, (P)Ltd., New Delhi
6.	Talc	Nice Chemicals,(P)Ltd., Kerala
7.	Magnesium Stearate	Nice Chemicals,(P)Ltd., Kerala
8.	Hydrochloric acid	Nice Chemicals,(P)Ltd., Kerala

✶ All other chemicals were of Analytical Grade.

EQUIPMENTS:

S.NO	NAME	MANUFACTURER
1.	Electronic Weighing Balance	A & D Company HR 200, Japan
2.	Single Punch Tablet Compression Machine	Cadmach Machinery Co. Pvt., Ahmadabad
3.	UV Visible Spectrophotometer	UV-1700 Pharmaspec, Shimadzu, Japan
4.	Digital Tablet Dissolution Test Apparatus	Disso 2000, Lab India, Mumbai
5.	Friability Test Apparatus	Indian Equipment Corporation, Mumbai
6.	Tablets hardness tester (Monsanto)	Praveen Enterprises, Bangalore
7.	Vernier Caliper	Linker, Mumbai
8.	X-ray machine	Stallion 20, Elpro International Ltd., India
9.	Differential Scanning Colorimeter	DSC Q200, Mumbai
10.	Fourier Transform Infrared Spectroscopy	Shimadzu, Japan
11.	High Performance Liquid Chromatography	Int L-C-GC Agilent Model, Japan
12.	Scanning Electron Microscopy	Hitachi S-3400, Japan
13.	Environmental Chamber	HTC 3003, Inlab Equipments (P) Ltd., India.

CHAPTER VIII

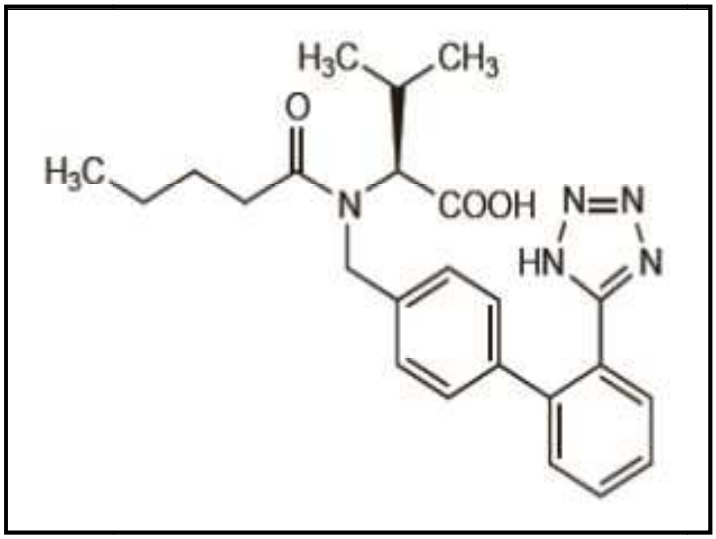
DRUG PROFILE

VALSARTAN

SYNONYM:

- Valsartaani, Valsartan, Valsatanum (Sean C Sweetman *et al*., 2009).

STRUCTURE: (Sean Sweetman *et al*., 2009; Anthony C Moffat, 2004)



SYSTEMATIC IUPAC NAME:

- N - (1 - oxopentyl) – N - [2'- (1 – h – tetrazol – 5 - yl) [1, 1'- biphenyl] – 4 - yl] – L-valine (Sean Sweetman *et al.,* 2009; Anthony C Moffat , 2004).

CHEMICAL FORMULA:

- $C_{24}H_{29}N_5O_3$ (Sean Sweetman *et al*., 2009; Anthony C Moffat, 2004).

DESCRIPTION:

Nature	:	White microcrystalline powder
Solubility	:	Freely soluble in ethanol, methanol, sparingly soluble in water.
Melting point	:	105 - 110°C
Molecular weight	:	435.519 g/mol
Log P (octanol/water)	:	1.499
Octanol/water partition coefficient	:	0.033
pKa	:	3.9 & 4.7 (Nadeem Siddiqui *et al*., 2011)

CATEGORY:

- ✶ Angiotensin II Receptor Antagonists.
- ✶ Antihypertensive Agents (Jennifer Martin and Henry Krum, 2002; Drug bank).

IDENTIFICATION:

- ✶ UV light absorption at 203, 248 nm (Nataraj K.S *et al*., 2011; Sean C Sweetman *et al*., 2009).

PHARMACODYNAMIC PROPERTIES:

Valsartan belongs to the family of angiotensin II type 1 receptor (AT_1) antagonists and possess about 20,000 fold greater affinities for it than for the angiotensin II type 2 receptor (AT_2). This action exert effects on blood pressure (BP) reduction, as well as decreases vascular smooth muscle contraction, inhibits sympathetic outflow, improves renal function and also leads to reduction in progression of atherosclerosis lesions

(Jennifier Martin *et al*., 2002). Also blockade of AT_1 receptor by valsartan leads to increase in local angiotensin II concentration that stimulates the unblocked AT_2 receptor. The increase in AT_2 receptor stimulation causes vasodilatation through local production of bradykinin which in turn leads to signaling cascade the increases the production of nitric oxide and cyclic guanosine 3'-5'-monophosphate at the endothelial level that provides protection against vascular dysfunction.

PHARMACOKINETIC PROPERTIES:

Absorption

- Rapidly absorbed after oral administration
- T max is 2 hour for parent compound, 5 to 9 hour for metabolite (Mehtap Saydam *et al*., 2007).

Metabolism

- Valsartan is not significantly metabolized in humans. The primary circulating metabolite, 4-OH-valsartan, is pharmacologically inactive and produced CYP2C9. 4-OH-valsartan accounts for approximately 9% of the circulating dose of valsartan. Although valsartan is metabolized by CYP2C9, CYP-mediated drug-drug interactions between valsartan and other drugs are unlikely (Drug Bank).

Excretion

- 83% excreted in the feces via biliary excretion.
- 13% in urine as unchanged drug (Mehtap Saydam *et al*., 2007).

PHARMACOKINETIC CHARACTERS OF VALSARTAN:

- ✶ Oral Bioavailability : 23 % with high variability.
- ✶ Half Life : Initial phase $t_{1/2}$ is <1 hour, terminal phase $t_{1/2\beta}$ is 5-9hour.
- ✶ Plasma protein binding : 94 to 97% mainly to albumin.
- ✶ Volume of Distribution : 17L
- ✶ Excretion : 83% in feces, 13% in urine (Drug Bank).

THERAPEUTIC INDICATIONS & USAGE:

- ✶ Hypertension
- ✶ Congestive Heart Failure
- ✶ Left ventricular dysfunction Post-myocardial infarction (MI) (Jennifier Martin & Henry Krum, 2002; Mehtap Saydam *et al*., 2007).

DOSING STRENGTH:

- ✶ ***Hypertension*:** Initial 80mg or 160mg once daily (OD); dose may be increased to achieve desired effect; maximum recommended dose: 320mg.
- ✶ ***Heart Failure* :** Initial 40mg twice daily (BID); titrate dose to 80-160mg twice daily, as tolerated; maximum daily dose: 320mg.
- ✶ ***Left ventricular dysfunction after MI:*** Initial 20mg twice daily; titrate dose to target of 160mg twice daily as tolerated (Access Medicine; Drug Bank).

ADVERSE EFFECTS:

- ✶ Dizziness (11.7%)
- ✶ Headache and Migraine (10.3%)
- ✶ Epistaxis (0.5%)
- ✶ Fatigue (10%)
- ✶ Rash (1.1%)
- ✶ Joint stiffness
- ✶ Muscle cramps
- ✶ Myalgia
- ✶ Orthostatic hypotension
- ✶ Hyperkalemia (5%)
- ✶ Respiratory tract disorders
- ✶ Nausea
- ✶ Vomiting (1.4%)
- ✶ Diarrhea
- ✶ Dyspnoea
- ✶ Dyspepsia
- ✶ Oedema (Nadeem Siddiqui *et al*., 2011).

DRUG INTERACTIONS:

- ✶ NSAIDS and Ciclosporin as it causes increased risk of renal impairment and hyperkalemia (Sean C Sweetman *et al*., 2009).
- ✶ General anesthetics, Clozapine, Dopamine agonists and other hypertensive causes increased risk of hypotension.

- ✶ Hyperkalemia can be caused during valsartan therapy with Potassium-sparing diuretics, Potassium supplements, ACE inhibitors and Heparin (Nadam Siddiqui *et al*., 2011)

CONTRAINDICATIONS:

- ✶ Severe hepatic impairment
- ✶ Liver cirrhosis
- ✶ Biliary obstruction
- ✶ Pregnancy
- ✶ Lactation (Mehtap Saydam *et al*., 2007).

DIETARY IMPLICATIONS:

- ✶ Avoid salt substitutes which contain potassium. May be taken with or without food (Drug Bank; Access Medicine).

STORAGE & COMPATIBILITY:

- ✶ Store at 25^0C (77^0F); excursions permitted to 15^0C to 30^0C (59^0F to 86^0F). Protect from moisture (Access Medicine).

GENERIC AVAILABLE:

- ✶ NO

FORMULATION TYPES:

- ✶ Conventional dosage forms of tablets and capsules
- ✶ Pulsatile capsule dosage form

- Fast dissolving tablets (Mehtap Saydam *et al*., 2007).

INTERNATIONAL BRAND NAMES:

- Diovan® (U.S, Canada, and multiple international markets)
- Varexan (Hung)
- Diovan HCT (Venez)
- Co-Diovan (Switz)
- Valaplex-D,Vartalan D (Chile)
- Diovan, Starval (India) (Sean C Sweetman *et al*., 2009).

ADDITIONAL INFORMATION

- Valsartan may have an advantage over losartan due to minimal metabolism requirements and consequent use in mild-to-moderate hepatic impairment (Drug Bank).

CHAPTER IX

EXCIPIENTS PROFILE

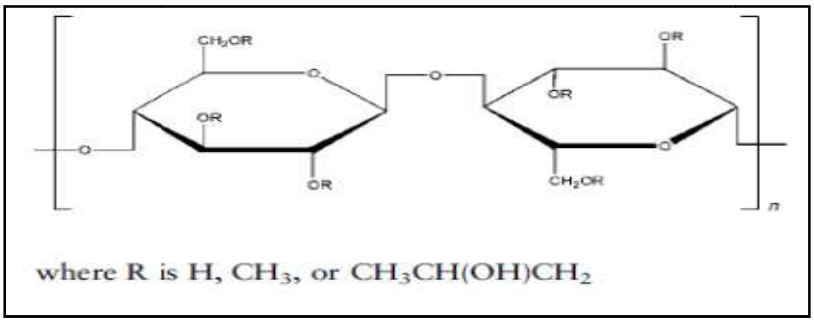
HYDROXY PROPYL METHYL CELLULOSE

(Raymond C. Rowe *et al*., 2006)

Synonym:

- ✶ Hypromellose
- ✶ Methocel

Structure:



Empirical formula:

- ✶ It is partly O-methylated and O-(2-hydroxy propylated) cellulose. (PhEur 2005). It is available in several grades depending upon the viscosity and extent of substitution.

Molecular weight:

- ✶ 10 000 – 1 500 000

Description:

- ✶ Color: White or creamy-white fibrous or granular powder.
- ✶ Odour: Odorless
- ✶ Taste: Tasteless

Melting point:

- 190–200^{0}C; chars at 225–230^{0}C.

Functional Category:

- Coating agent.
- Film- former.
- Stabilizing agent.
- Tablet binder.
- Viscosity increasing agent.

Typical Viscosity values for 2 % (w/v) aqueous solutions of different viscosity grades of HPMC at 20°C

Methocel K100 Premium LVEP	100
Methocel K4M Premium	4000
Methocel K15M Premium	15000
Methocel K100M Premium	100 000
Methocel E4M Premium	4000
Methocel F50 Premium	50
Methocel E10M Premium CR	10 000
Methocel E3 Premium LV	3
Methocel E5 Premium LV	5
Methocel E6 Premium LV	6
Methocel E15 Premium LV	15
Methocel E50 Premium LV	50
Metolose 60SH	50, 4000, 10 000
Metolose 65SH	50, 400, 1500, 4000
Metolose 90SH	100,400,4000, 15 000

Solubility:

- ✶ Soluble in cold water, forming a viscous colloidal solution,
- ✶ Practically insoluble in chloroform, ethanol (95 %) and ether,
- ✶ Soluble in mixtures of ethanol and dichloromethane,
- ✶ Soluble in mixtures of water and alcohol.

Storage Conditions:

- ✶ It should be stored in a well-closed container, in a cool, dry place.

Handling Precautions:

- ✶ Hypromellose dust may be irritant to the eyes and eye protection is recommended
- ✶ Excessive dust generation should be avoided to minimize the risks of explosion.
- ✶ Hypromellose is combustible.

Regulatory status:

- ✶ Included in the FDA inactive ingredients. Recognized by GRAS status.

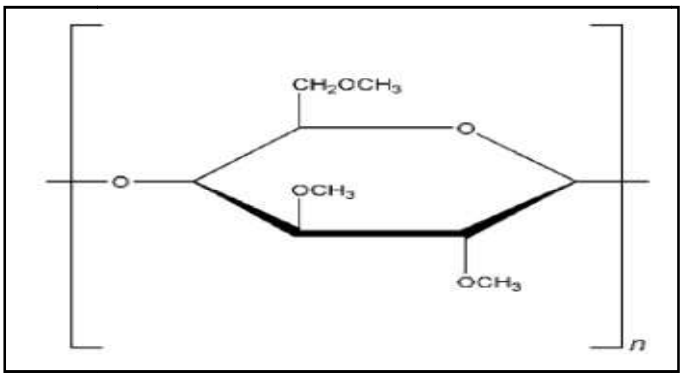
METHYL CELLULOSE

(Raymond C. Rowe *et al*., 2006)

Synonym:

- Benecel
- Metolose

Structure:



Empirical formula:

- Long-chain substituted cellulose containing approximately 27 – 32 % of the hydroxyl group in the form of methyl ether.

Molecular weight:

- 10 000 – 220 000 Dalton.

Description:

- Color: White, fibrous powder or granules.
- Odour: Practically odorless and
- Taste: Tasteless.

Melting Point:

- 190–200°C.

Solubility:

- Practically insoluble in acetone, methanol, chloroform, ethanol (95 %), ether, saturated salt solutions, toluene and hot water.
- In cold water, it swells and disperses slowly to form a clear to opalescent, viscous, colloidal dispersion.

Functional Category:

- Bulk laxative (5.0 – 30.0 %).
- Emulsifying agent (1.0– 5.0 %),
- Tablet binder (1.0 – 5.0 %).
- Tablet Coating (0.5 -5.0 %).
- Tablet and capsule disintegrate (2.0 – 10.0 %).

Storage Conditions:

- It should be stored in an airtight container in a cool, dry place.

Handling Precautions:

- Irritant to the eyes & eye protection should be worn.
- Methylcellulose is combustible.
- Spills of the dry powder or solution should be cleaned up immediately, as the slippery film that forms can be dangerous.

Regulatory status:

- Included in the FDA inactive ingredients. Recognized by GRAS status.

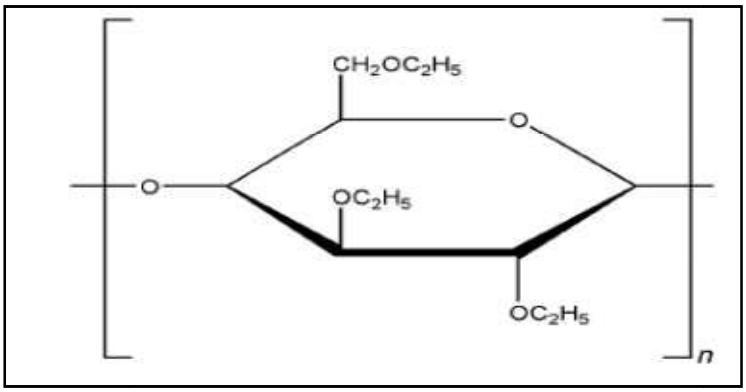
ETHYL CELLULOSE

(Raymond C. Rowe *et al*., 2006)

Synonyms:

- Aquacoat ECD
- Aqualon
- Ethocel
- Surelease

Structure:



Empirical formula:

- $C_{12}H_{23}O_6(C_{12}H_{22}O_5)_nC_{12}H_{23}O_5$

Molecular weight:

- 40 0000

Description:

- Color: White to light tan colored powder.
- Odour: Odorless.
- Taste: Tasteless.

Melting point:

- ✶ 165^0 - 185^0 C

Solubility:

- ✶ Practically insoluble in propylene glycol, glycerine and water
- ✶ Freely soluble in chloroform, ethanol, ethyl acetate, methanol and toluene.

Functional Category:

- ✶ Coating agent.
- ✶ Flavouring fixative.
- ✶ Tablet binder.
- ✶ Tablet filler.
- ✶ Viscosity-increasing agent.

Storage Conditions:

- ✶ It should be stored at a temperature not exceeding 328^0 C (90^0F) in a dry area away from all sources of heat.

Handling Precautions:

- ✶ To prevent fine dust clouds of ethyl cellulose from reaching potentially explosive levels in the air.
- ✶ Its combustible
- ✶ It may be an irritant to the eyes and eye protection should be worn.

Regulatory status:

- ✶ Included in the FDA inactive ingredients. Recognized by GRAS status.

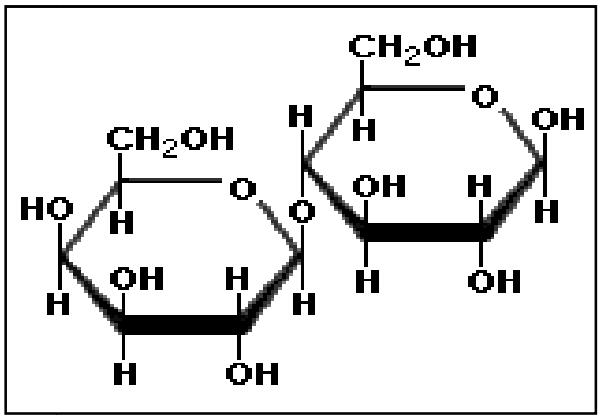
LACTOSE

(Raymond C. Rowe *et al*., 2006)

Synonym:

- Lactopress Anhydrous.
- Lactosum.
- Milk sugar.

Structure:



Empirical formula:

- $C_{12}H_{22}O_{11}$

Molecular weight:

- 342.30

Description:

- White to off-white crystalline particles or powder.

Melting Point:

- ✶ 223^0 -252.2^0 C

Solubility:

- ✶ Soluble in water,
- ✶ Sparingly soluble in ethanol (95 %) and ether.

Functional Category:

- ✶ Binding agent.
- ✶ Directly compressible excipient.
- ✶ Lyopholization aid.
- ✶ Tablet and capsule filler.

Storage Conditions:

- ✶ It should be stored in a well-closed container in a cool, dry place.

Handling Precautions:

- ✶ Excessive generation of dust, or inhalation of dust, should be avoided.

Regulatory status:

- ✶ Included in the FDA inactive ingredients. Recognized by GRAS status.

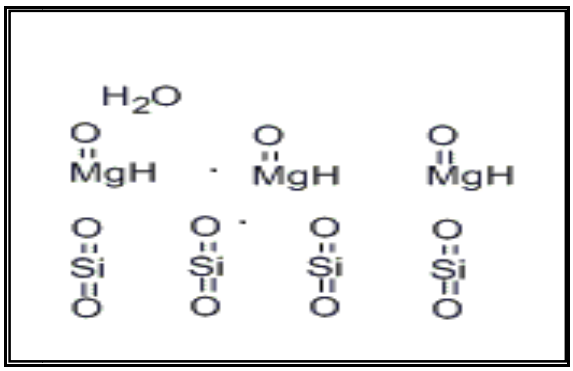
TALC

(Raymond C. Rowe *et al*., 2006)

Synonyms:

- Powdered talc.
- Purified French chalk.
- Soapstone.

Structure:



Empirical formula:

- $Mg_6(Si_2O_5)_4(OH)_4$

Description:

- Appearance: Very fine, unctuous, crystalline powder.
- Color: White to grayish-white.
- Odour: Odorless, impalpable.

Solubility:

- ✶ Practically insoluble in dilute acids and alkalis, organic solvents, and water.

Storage Conditions:

- ✶ It should be stored in a tightly closed container in a cool and dry place.

Functional Category:

- ✶ Anti caking agent.
- ✶ Glidant.
- ✶ Lubricant.

Handling Precautions:

- ✶ Talc is irritant if inhaled and prolonged excessive exposure may cause pneumoconiosis.

Regulatory Status:

- ✶ Included in the FDA inactive ingredients. Recognized by GRAS status.

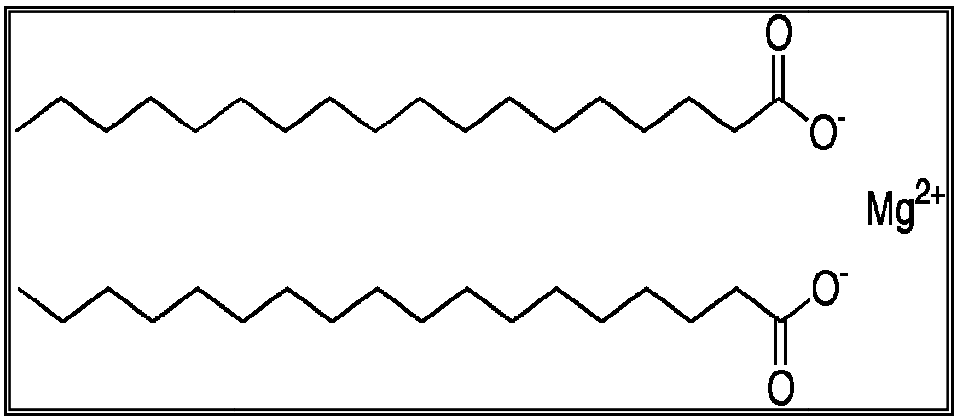
MAGNESIUM STEARATE

(Raymond C. Rowe *et al.,* 2006)

Synonyms:

- Magnesium octadecanoate.
- Octadecanoic acid.
- Magnesium salt.

Structure:



Empirical formula:

- $C_{36}H_{70}MgO_4$

Molecular Weight:

- 591.34

Melting Point:

- 117–150^{0}C (commercial samples).
- 126–130^{0}C (high purity magnesium stearate).

Description:

- ✶ It is a very fine powder.

Solubility:

- ✶ Insoluble in ethanol, ether and water.
- ✶ Slightly soluble in warm benzene and warm ethanol 95%.

Storage Conditions:

- ✶ It is stable and should be stored in a well closed container, in a cool, dry place.

Functional Category:

- ✶ Tablet and capsule lubricant.

Handling Precautions:

- ✶ Eye protection and gloves are recommended.
- ✶ Excessive inhalation of magnesium stearate dust may cause upper respiratory tract discomfort, coughing, and choking.
- ✶ Magnesium stearate should be handled in a well ventilated environment; a respirator is recommended.

Regulatory Status:

- ✶ Included in the FDA inactive ingredients. Recognized by GRAS status.

CHAPTER X
EXPERIMENTAL PROTOCOL

I. STANDARD CALIBRATION CURVE OF VALSARTAN

(a) Preparation of dissolution medium:

0.1N Hydrochloric Acid:

Dissolve 8.5ml of concentrated hydrochloric acid in 1000ml of distilled water to get 0.1N hydrochloric acid (Mahajan P *et al.,* 2011; Marget Chandira *et al*., 2009).

(b) Determination of (Absorption Maximum) λ_{max} by UV Spectrum:

UV spectrum is obtained for 10µg/ml concentration of valsartan using standard buffer solution (0.1N hydrochloric acid).

(c) Preparation of standard calibration curve for valsartan:

A known quantity of valsartan (50mg) is accurately weighed and dissolved in a small quantity of methanol and made upto 50ml with the 0.1N hydrochloric acid. From this primary stock solution 10ml is pipette out and made upto 100ml with 0.1N hydrochloric acid. From this secondary solution aliquots are taken to produce 2, 4, 6, 8, 10, 12, 14, 16, 18, 20µg/ml and diluted to 100ml with 0.1N hydrochloric acid.

The absorbance of the resulting solution is measured at 204nm by UV-Visible Spectrophotometer (Shimadzu UV-1700 Pharma spec, Japan) using 0.1N hydrochloric acid as blank. The standard curve is plotted by taking concentration in X-axis and absorbance in Y-axis. The calibration curve is used for the estimation of the concentration of drug released during the *in vitro* dissolution studies (Sevgi tatar *et al*., 2002).

II. PREFORMULATION (COMPATABILITY) STUDIES:

The compatibility studies are carried out by DSC and FT-IR in order to evaluate the drug and polymer interaction.

(a) Differential Scanning Calorimetric (DSC) Studies:

DSC is performed using DSC Q200 Thermal Analyzer. The instrument is calibrated with indium standard. Accurately weighed (it varies from 3mg-5mg) (Kyriakos Kachrimanis *et al*., 2011) samples are placed in an open type ceramic sample pans. Thermo grams are obtained by heating the sample at a constant heating rate of 10^0 C/minute. A dry purge of Argon gas (25ml/min) is used for all runs. Samples are heated from 37°C -400°C (Mahajan P *et al*., 2011).

(b) Fourier Transform Infrared Spectroscopic (FT-IR) Studies:

The possibility of drug-excipient interactions are further investigated by FT-IR. The FT-IR graph of pure drug and combination of drug with excipient are recorded. The analysis is performed by using FT-IR Spectrometer (Shimadzu, Japan). The scanning range is 450-4000 cm^{-1} and the resolution is $4cm^{-1}$. Samples are prepared in KBr pellets (Debajyoti Ray et al., 2010; Kyriakos Kachrimanis *et al*., 2011; Praveen Kumar Mandapalli *et al*., 2012).

III. FORMULATION OF VALSARTAN FLOATING MATRIX TABLETS:

Non-effervescent floating matrix tablets containing valsartan are prepared by direct compression technique using varying concentrations of different grades of polymers. All the ingredients are accurately weighed and passed through different mesh sieves accordingly. Then, except magnesium stearate all other ingredients are blended uniformly in glass mortar. After sufficient mixing of drug as well as other components,

magnesium stearate and talc is added, as post lubricant, and further mixed for additional 2-3 minutes. 250mg of powder blend is weighed and compressed into 10mm biconvex tablets by using a single punch tablet machine (Cadmach, Ahmedabad). The weights of the tablets are kept constant for all formulation (Pare A *et al*., 2008).

IV. EVALUATION OF VALSARTAN FLOATING MATRIX TABLET:

1. PRECOMPRESSIONAL EVALUATION OF POWDER BLEND:

(a) Angle of repose (θ):

The frictional forces in a loose powder or granules can be measured by angle of repose. This is the maximum angle possible between the surface of a pile of powder or granules and the horizontal plane (Natasha Sharma *et al.,* 2011). The granules are allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose is then calculated by measuring the height and radius of the heap of granules formed (Ajay Bagherwal *et al*., 2010; Leon Lachman *et al*., 2009; Margret Chandira *et al*., 2009).

$$\tan \theta = h/r$$

$$\theta = \tan^{-1} (h/r)$$

Where,

θ = angle of repose

h = height of the heap

r = radius of the heap

The relationship between Angle of repose and powder flow is as follows in table.

Angle of Repose	Powder flow
< 25°	Excellent
25°- 30°	Good
30°- 40°	Passable
> 40°	Very Poor

(b) Bulk density:

Bulk density is the ratio between a given mass of powder and its bulk volume. Apparent bulk density is determined by pouring the weighed granules into a graduated cylinder via funnel and measuring the volume (Natasha Sharma *et al*., 2011; Margret Chandira *et al*., 2009). Density is calculated by using the formula,

$$\text{Bulk density} = \frac{\text{Mass of the powder}}{\text{Bulk volume of the powder}} = \frac{W}{V_o}$$

(c) Tapped density:

Tapped density is the ratio between a given mass of powder and the constant or final volume of powder after tapping. It is determined by tapping a graduated cylinder containing a known mass of granules for a fix number of taps until the powder volume has reached a constant value (Natasha Sharma *et al*., 2011; Shyamala Bhaskaran, 2010). The tapped density is computed by using the formula,

$$\text{Tapped density} = \frac{\text{Mass of the powder}}{\text{Minimum (tapped) volume of the powder}} = \frac{M}{V_f}$$

(d) Compressibility Index: (I)

The flow ability of powder can be evaluated by comparing the bulk density (ρ_o) and tapped density (ρ_t) of powder and the rate at which it packed down (Natasha Sharma *et al*., 2011) Compressibility index is calculated by using the formula,

$$\textbf{Compressibility Index (\%)} = \frac{\rho_t - \rho_o}{\rho_t} \times 100$$

Where,

ρ_o = Bulk density g/ml.

ρ_t = Tapped density g/ml.

Values of I: (Debajyoti Ray *et al*., 2010; Shyamala Bhaskaran, 2010)

Compressibility Index	Type of flow
5-15%	Excellent
15-25%	Good
>25%	Extremely poor

(e) Hausner's Ratio:

The Hausner's ratio is a number that is correlated to the flowability of a powder or granular material (Debajyoti Ray *et al*., 2010; Shyamala Bhaskaran, 2010; Margret Chandira *et al*., 2009). It is calculated by the formula,

$$\text{Hausner ratio} = \frac{\rho_t}{\rho_o} \times 100$$

Where,

ρ_o = Bulk density g/ml.

ρ_t = Tapped density g/ml.

The values less than 1.25 indicate good flow (= 20% Carr), whereas greater than 1.25 indicates poor flow (= 33% Carr). Between 1.25 and 1.5, added glidant normally improves flow.

(f) Estimation of drug content for powder blend:

10mg drug equivalent of powder blend is dissolved in 10ml of methanol and the volume is made up to 100ml with 0.1N hydrochloric acid. The solution is filtered and 10ml of filtrate is diluted to 100ml with 0.1N hydrochloric acid (Arunkumar *et al*., 2008). The absorbance of the resulting solution is measured at λ_{max} (204nm) using UV spectrophotometer and the drug content is estimated.

2. POSTCOMPRESSIONAL EVALUATION OF VALSARTAN FLOATING TABLET:

(a) General appearance:

The formulated tablets are evaluated for general appearance Viz color, shape, appearance (Leon Lachman *et al*., 1987).

(b) Hardness:

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets is determined by using Monsanto hardness tester

(Leon Lachman *et al*., 1987). It is expressed in kg/cm^2. Three tablets are randomly picked and hardness of the tablets is determined (Debajyoti Ray *et al*., 2010).

(c) Thickness and Diameter:

Thickness of the tablet mainly depends upon the filling, physical properties of material to be compressed and compression force. Vernier caliper (Mina Ibrahim Tadros, 2010) is used to measure tablet thickness and diameter (Natasha Sharma *et al*., 2011). Three tablets are randomly picked from each batch and the thickness and diameter of the tablets are determined. Both should be controlled within a ±5% variation of a standard value.

(d) Friability Test:

The friability of tablets is determined by using Roche Friabilator. It is expressed in percentage (%). Twenty tablets are initially weighed ($W_{initial}$) and transferred into friabilator. The friabilator is operated at 25rpm for 4 minutes or run up to 100 revolutions (Debajyoti Ray *et al*., 2010; Margret Chandira *et al*., 2009; Mina Ibrahim Tadros, 2010). The tablets are weighed again (W_{final}). The % friability is then calculated by,

$$\text{Percentage Friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

Percentage friability of tablets <1% was considered acceptable (Leon Lachman, 1987).

(e) Weight variation Test:

Twenty tablets are selected randomly from each formulation and weighed individually and the average weight is calculated as per I.P method. Not more than two

tablets should deviate from the percentage as given in IP and none should deviate by more than twice that percentage (Ajay Bagherwal *et al*., 2010).

The following percentage deviation in Weight Variation is shown in table (Margret Chandira *et al*., 2009; IP 2007).

Average Weight of a tablet	**Percent Deviation**
80mg or less	±10%
More than 80mg but less than 250mg	±7.5%
250mg or more	±5%

(f) Estimation of drug content for tablets:

10 mg drug equivalent of the powdered formulation is dissolved in 5ml of methanol, made up to 100ml with 0.1N hydrochloric acid and filtered. 10ml of the filtrate is made up to 100ml with 0.1N hydrochloric acid. 10µg/ml solution is prepared from the above solution and analyzed for drug content by UV spectrophotometer at a λ_{max} 204 nm (Arunkumar N *et al*., 2008).

***3. IN VITRO* BUOYANCY STUDIES:**

The tablets are placed in a beaker containing 100ml of 0.1N hydrochloric acid maintained at 37°C (Shreeraj H. Shah *et al*., 2010; Sakarkar D. M. *et al*., 2010). The time required for the tablet to rise to the surface and float is determined as floating lag time and the time period up to which the tablet remained floating is determined as total floating time (Arunkumar N *et al*., 2008; Praveen Kumar N *et al.,* 2008).

4. SWELLING STUDIES:

The swelling behavior of a dosage form is measured by studying its weight gain or water uptake. The dimensional changes could be measured in terms of the increase in tablet diameter and/or thickness over time. Swelling is a vital factor to ensure buoyancy and dissolution of floating matrix tablet (Shishu *et al*., 2007; Margret Chandira *et al*., 2009). Swelling index of tablet is determined for each formulation; tablets are weighed and placed in a beaker containing 200ml of 0.1N hydrochloric acid at room temperature (Mina Ibrahim Tadros, 2010). After each hour the tablet is removed from the beaker, blotted with filter paper to remove excess of water and weighed again upto 12 hours. Water uptake is measured in terms of percent weight gain, as given by the equation (Sakarkar *et al*., 2010; Debajyoti Ray *et al*., 2010).

$$\text{Swelling Index (\%)} = \frac{W_t - W_0}{W_0} \times 100$$

Where,

W_t = weight of tablet at time t hour

W_o = weight of tablet before immersion

***5. IN VITRO* RELEASE STUDIES:**

In vitro release studies are performed in USP type II paddle apparatus for 12 hours. The tablets are placed in the dissolution medium of 900 ml 0.1N hydrochloric acid in the dissolution apparatus. The paddle is rotated at 50 rpm maintained at 37 ± 5°C (Mahajan P *et al.,* 2011; Praveen Kumar Mandapali *et al*., 2012). 5 ml samples are withdrawn at every 15 minutes intervals for the first hour and every 30 minutes intervals for the next 11hours. The same volume of buffer solution is replaced into the dissolution

medium. The withdrawn samples are diluted up to 50ml with 0.1N hydrochloric acid. Samples are analyzed at 204 nm using UV spectrophotometer (USP 30-NF, 2007; Amit Kumar Nayak *et al*., 2011). The studies are done in triplicate.

SUMMARY OF GENERAL DISSOLUTION CONDITIONS

Parameter	***Specifications***
Dissolution medium	Buffer 0.1N hydrochloric acid
Temperature	37.0 ± 0.5 °C
Initial Volume	900ml
Rotation speed	50rpm
Drawn Volume	5ml
Running time	12 hrs in 0.1N hydrochloric acid
Medium Replacement	Media refilling at every 30 min.

6. *INVITRO* DRUG RELEASE KINETICS STUDIES:

In controlled or sustained release formulations the three most important rate controlling mechanisms are,

- ✶ Diffusion
- ✶ Swelling and
- ✶ Erosion

The *In vitro* release profiles obtained from the floating tablets were fitted to zero order, first order, Higuchi, Hixson Crowell, Korsemeyer & Peppas model kinetics, to find out the mechanism of drug release (Pramod Patil *et al.,* 2011; Amit Kumar Nayak *et al*., 2011).

Release Kinetics Model	*Equation*
Zero Order	$Q_t = Q_0 + K_0.t$
First Order	$In\ Q_t = In\ Q_0 + K_0.t$
Hixson-Crowell	$Q_0^{1/3} - Q_t^{1/3} + K.t$
Higuchi	$Q = KH.\ t^{1/2}$
Korsmeyer - Peppas	$M_t / M_0 = a.tn$

Fitness of release profiles to linear equations is assessed by comparing the coefficients of determination (r) values.

For cylinder type of systems, (Harris Shoaib *et al*., 2006; Praveen Kumar Mandapali *et al*., 2012).

Diffusion Exponent (n)	*Overall Solute Diffusion Mechanism*
n < 0.45	Classical Fickian diffusion
n=0.45 to 0.89	Anomalous Non Fickian transport i.e. coupled drug diffusion in the hydrated matrix and polymer relaxation (Indicators of both phenomenon)
n=0.89	Case II relaxation release transport - zero order release (Polymer relaxation or swelling controlled systems)
n> 0.89	Super Case II transport

The *in-vitro* release data are fitted to the above mathematical models and the applying data are,

- ✶ Cumulative % drug release vs. time for zero order kinetic.
- ✶ Log cumulative of % drug remaining vs. time for first order kinetic.
- ✶ Cumulative % drug release vs. Square root of time for Higuchi model.
- ✶ Log cumulative % drug release vs. log time for Korsmeyer-peppas model and
- ✶ Cube root of drug % remaining in matrix vs. time for Hixson-Crowell cube root law.

V. SELECTION OF BEST FORMULATION:

The best formulation is selected depending on the results obtained from floating behavior, *Invitro* release studies and kinetic analysis.

A) EVALUATION OF BEST FORMULATION

1. *COMPARISON WITH MARKETED FORMULATION*

The release of the best formulation is compared with the marketed formulation (Pare A *et al*., 2008; Mahajan P *et al*., 2011).

2. *ASSAY BY HPLC METHOD*

Quantitative determination of valsartan is performed by high performance liquid chromatography method (HPLC-Int L-C-GC Agilent Model) (Ramesh C. Nagarwal *et al*., 2010; Ziyaur Rahman *et al*., 2006). Fifteen tablets are taken and crushed to powder with mortar and pestle. Exact amount of powder (average weight) is taken and diluted with methanol upto 50ml in a volumetric flask. After sonication for 15mts, solution is filtered through 0.45µm filter paper. The total amount of drugs within the tablets are analyzed after appropriate dilution of test solution by using the HPLC method as described below

against the reference solution of valsartan pure powder prepared in the same procedure (Liandong Hu *et al*., 2010 ; Gendle R *et al.,* 2010 ; Uttam Mandal *et al*., 2007)

- **Column :** Stainless steel column (25cmx4.6mm) and packed with octadecylsilane bonded to porous silica (5µm particle size).
- **Mobile Phase :** A mixture of 50 volumes of water, 50 volumes of acetonitrile and 0.1 volumes of glacial acetic acid (50:50:0.1) (USP 30-NF 25, 2007).
- **Detector:** UV detection with 273nm (UV-Visible Spectrophotometric-Shimadzu).
- **Injection Volume:** 10µl.
- **Flow Rate:** 1ml per minute.

3. ***SCANNING ELECTRON MICROSCOPY***

The SEM image of the tablet has been used to examine surface topography; texture and morphology of fractured surface are compared to hypothesize the mechanism of drug release and floating.

The surface of the tablets is studied by SEM. The preparation of the samples are accomplished by placing the intact tablets before and after 12 hours dissolution, by drying them to remove water content and placing these tablets on specimen holder. The samples are coated with a gold-palladium target using a Novatec vaccum evaporator for 15minutes (Vandana Jugran *et al*., 2011). SEM images are obtained at an acceleration voltage of 8 to 10KV. Study of the morphology of the particles using SEM is done, which provides information about the 3-D structure of the particles with the resolution power up to 5^0 A. Imaging is done at a magnification of 200µm and pressure of 0.98 torr (Anilkumar *et al*., 2010; Manoj N *et al*., 2007).

4. In vivo X – RAY STUDIES:

The *in vivo* studies approved by Institutional Animal Ethical Committee Reference No. 14024/E1/4/2011 and are performed on healthy albino rabbit weighing 2-2.5 kg. The animal is fasted overnight but allowed to take water ad libitum (Londhe S *et al*., 2010). Then 30 ml of 5 % dextrose solution is given immediately before administering the tablets by using stomach tube (No. 12 French catheter) and 20 ml syringes.

The tablets are made opaque by incorporating barium sulphate ($BaSO_4$) instead of drug. The rabbit is exposed to X-ray imaging in the abdominal region, and photographs are taken at 0, 2, 4, 6, 8, 10 & 12 hrs after administration of tablet. At hourly intervals 30 ml of 5% dextrose solution is given to maintain optimum fluid level in the stomach (Dinesh Kumar *et al*., 2010). The gastric residence time is observed.

5. STABILITY STUDIES:

Stability studies are performed as per the ICH and WHO guidelines to determine the result of aging and storage under various conditions. The best formulation of valsartan floating matrix tablet is subjected to stability studies. The optimized formulation is stored at temperature of $40^0C \pm 2^0C$ and relative humidity of 75% ± 5% in an environmental chamber for a period of three months (Mina Ibrahim Tadros *et al.,* 2010; Jadhav Mayur N *et al.,* 2010; Pramod Patil *et al.,* 2011). The formulation is evaluated for its appearance, hardness, floating lag time and drug content analysis at every one month interval.

CHAPTER XI
RESULTS AND DISCUSSION

I. STANDARD CALIBRATION CURVE OF VALSARTAN:

(a) Preparation of dissolution medium:

The preparation of dissolution medium was prepared by using 0.1N hydrochloric acid.

(b) Determination of (Absorption Maximum) λ_{max} by UV Spectrum:

The λ_{max} of valsartan was determined by scanning the 10µg/ml of the drug solution in 0.1N hydrochloric acid. It showed the λ_{max} at 204nm in 0.1N hydrochloric acid. The λ_{max} of valsartan was showed in UV spectrum (Figure: 1).

(c) Preparation of standard calibration curve for valsartan:

Linear correlation coefficient was obtained for calibration of valsartan in 0.1N hydrochloric acid. Valsartan obeys the Beer's law within the concentration range 2 to 20 µg/ml. The correlation coefficient was found to be $\gamma = 0.99980$. Calibration plot of valsartan in 0.1N hydrochloric acid was shown in Table: 1 & Figure: 2.

II. PREFORMULATION (COMPATABILITY) STUDIES:

(a) Differential Scanning Calorimetric (DSC) Studies:

The DSC studies were carried out to detecting the drug-polymer incompatibility. The DSC thermo grams of pure drug & different polymers were shown in the Figure: 3.

The DSC thermo grams of pure drug valsartan showed an endothermic peak indicating the melting point 105 - 110°C which is in total agreement with literature value of the drug (Nadeem Siddiqui *et al*., 2011). An endothermic peak corresponding to the melting point of pure drug was prominent in all the drug-polymer mixture. From this

observation we can draw a conclusion that the drug is not showing any type of interaction with the polymers.

(b) Fourier Transform Infrared Spectroscopic (FT-IR) Studies:

FT-IR studies were carried out to confirm the compatibility between pure drug and polymers. The spectra obtained from the FT-IR studies from 450-4000 cm^{-1} . The FT-IR spectrum of the drug & polymers were shown in the Figure: 4. The comparison of IR spectrum of pure drug with IR spectra of polymers showed no appreciable change in the positions of characteristic absorption band.

The FT-IR Spectra of pure drug valsartan shows as follows,

S. NO	CHARACTERISTICS	WAVENUMBER ($^{cm-1}$)
1.	N-H Stretching	3443.05
2.	C-H Stretching in Alkane	2964.69
3.	C=O Stretching	1730.21
4.	Ar C=C Stretching	1600.97
5.	Isopropyl Stretch	1469.81
6.	CH_3 Bending	1410.01
7.	C-N Stretching	1274.99
8.	C-C Stretching	1205.55
9.	p- substituted benzene	852.56

All the major bands present in the spectrum of the pure drug are clearly observed in the spectrum of polymers with negligible changes in their position. This study clearly suggests that the pure drug remains in its normal form and hence there was no interaction between the drug and polymer.

III. FORMULATION OF VALSARTAN FLOATING MATRIX TABLETS:

The valsartan floating matrix tablets were prepared by non-effervescent method using the hydrophilic and hydrophobic polymers. Both polymers were chosen as they are well established in the similar studies and have great swelling and sustained release properties respectively. From the trial studies, the formula was optimized depending on the floating behavior of the tablets and the optimized formulas were given in the Table: 2A & 2B. It was found that the tablets showed good floating behavior at the concentration of 20-75% of the polymers. Various grades of HPMC (HPMC K100M, HPMC K15M, HPMC K4M), and their combination with ethyl cellulose showed better floating behavior at concentration 80%, while methylcellulose and their combination with ethyl cellulose showed better floating behavior at concentration 75%.

The floating lag time was inversely related to the concentration of polymers and the formula was optimized accordingly.

IV. EVALUATION OF VALSARTAN FLOATING MATRIX TABLET:

1. PRECOMPRESSIONAL EVALUATION OF POWDER BLEND:

The powder blend of all the formulations was evaluated for the precompression parameters such as angle of repose, bulk density, tapped density, compressibility index, Hausner's ratio, and percentage drug content.

(a) Angle of repose (θ):

The angle of repose for the formulated powder blend was found to be in the range of 27º.08' to 30º.26', which indicates good flow properties of powder blend. The results were shown in Table: 3A & 3B & Figure: 5A.

(b) Bulk density:

The bulk density of the powder blend was in the range of 0.250 g/ml to 0.367 g/ml, which indicates that the powder blend were not bulky. The results were shown in Table: 3A&3B & Figure: 5B**.**

(c) Tapped density:

The tapped density of the powder blend was in the range of 0.290 g/ml to 0.480 g/ml. The results were shown in Table: 3A &3B & Figure: 5C.

(d) Compressibility Index: (I)

Compressibility index were found to be in between 14% to 25.03%, which indicates that the powder blend have the required flow property for compression. The results were shown in Table: 3A &3B & Figure: 5D.

(e) Hausner's Ratio:

The Hausner's ratio of the powder blend was found to be in the range 1.16 to 1.25, which indicates good flow properties of powder blend. The results were shown in Table: 3A &3B & Figure: 5E.

(f) Estimation of drug content for powder blend:

The percentage drug content for F1 to F20 formulations were found to be in between 98.32% to 99.79%, ensured the uniformity of drug content. The results were shown in Table: 3A&3B.

From the above results it was concluded that the angle of repose (< 30º) indicate good flow properties of the powder blend. This was further supported by lower compressibility index values (<25%) results in good to excellent flow properties. Powder density and hardness were often interrelated properties. In addition, powder density may

influence compressibility, tablet porosity, dissolution, and other properties. All these results indicate that the powder blend of all the formulations possessed satisfactory flow properties (Amit K. Jain *et al*., 2011).

2. POSTCOMPRESSIONAL EVALUATION OF VALSARTAN FLOATING TABLET:

Tablets of different formulations were subjected to evaluation tests such as general appearance, hardness, thickness, diameter, friability, weight variation and drug content.

(a) General appearance:

The formulated tablets were white color, biconvex and round shaped without any scoring on any sides. All tablets were elegant in appearance. The results were shown in Table: 4A & 4B.

(b) Hardness:

The hardness of all the formulations were measured by Monsanto tester and was found to be in the range of 3.5 – 4 kg/cm^2, which indicates good mechanical strength with an ability to withstand physical and chemical stress conditions while handling. The results were shown in Table: 4A & 4B.

(c) Thickness and Diameter:

The thickness and diameter of all the formulations were measured by vernier caliper and were ranged between 3.5 – 4mm & 10mm, indicates that the tablets having uniform particle size distribution and no deformity. The results were shown in Table: 4A & 4B.

(d) Friability Test:

The percentage friability of all the formulations were in between 0.13% to 0.50%. The percentage friability was less than 1% in all the formulations, which indicates good mechanical resistance of the tablet. The values of Hardness test and Percentage friability indicates good handling property of prepared tablets. The results were shown in Table: 4A & 4B.

(e) Weight variation Test:

The weight variation tests were performed according to the procedure given in the pharmacopeia. All the formulated (F1 to F20) tablets passes weight variation test as the percentage weight variation was within the pharmacopoeia limits of ±5% of the weight and hence all the formulations passes the weight variation within the acceptable limits as per I.P. The results were shown in Table: 4A & 4B.

(f) Estimation of drug content for tablets:

The percentage drug content of all the formulations were within the range from 99.16% to 99.89%, showed that the drug was uniformly distributed in all the formulations**.** Hence the percentage drug content of all the formulations complies with official specifications as per U.S.P (Limits: not less than 90% and not more than 110%). The results were shown in Table: 4A, 4B & Figure: 5F.

From the above results, it was concluded that all the formulations showed acceptable pharmacopeia properties and complied with the pharmacopeia specifications for weight variation, drug content, and friability (Amit K. Jain *et al*., 2011; U.S.P 30 NF 2007).

3. IN VITRO BUOYANCY STUDIES:

The time taken for a dosage form to emerge on the surface of medium called Floating Lag Time (FLT) or Buoyancy Lag Time (BLT) and total duration of time by which dosage form remains buoyant is called Total Floating Time (TFT) (Ravikumar *et al*., 2009; Riteshkumar *et al*., 2010; Margret Chandria *et al*., 2009).

Among the twenty formulations, the formulations F1 – F15 (containing various grades of HPMC (HPMC K100M, HPMC K4M, & HPMC K15M) alone and it's combined with ethyl cellulose) Floated immediately.

The formulation F16 (containing methylcellulose alone) had a lag time of 10minutes. The formulations F17 – F20 (containing the Combination of methylcellulose and ethyl cellulose) had a lag time of 3 – 10 minutes. All the formulations remained buoyant upto 24hours. The results were shown in Table: 5A & 5B & Figure: 6.

With reference to buoyancy studies results it can be concluded that the batch containing HPMC polymers alone and its combination with ethyl cellulose showed good floating lag time when compared to batch containing methylcellulose polymers alone and its combination with ethyl cellulose. The buoyancy of the tablet varies from polymer to polymer which is governed by both the swelling of the hydrocolloid upon contact with the dissolution fluid and the presence of voids in the centre of the tablet (Ramesh C. Nagarwal *et al*., 2010).

4. SWELLING STUDIES:

Swelling study was performed on all the batches (F1 – F20) for 12hours. The results of swelling index were given in the Table No: 6A & 6B. While the plot of the swelling index against time (hr) is shown in Figure: 7 & 8.

Swelling index was calculated with respect to time. As time increases, the swelling index was increased, because weight gain by tablet was increased proportionally with rate of hydration. Later on, it decreased gradually due to dissolution of outermost gelled layer of tablet into dissolution medium (Margret Chandira *et al*., 2010; Amit Jain *et al*., 2011).

(a) Effect of hydrophilic polymers on swelling index:

The percentage swelling index of formulations (F1-HPMC K100M, F6-HPMC K4M, F11-HPMC K15M and F16-Methylcellulose) containing hydrophilic polymers were found to increase in the following order.

HPMC K100M > HPMC K15M > HPMC K4M > MC

The hydrophilic polymers formed a gel layer around the tablet when they contact with water. This is due to the penetration of solvent into the free spaces between macromolecular chains of polymer and so the dimension of the polymer molecule was increased (swelling) due to polymer relaxation caused by stress of the penetrated solvent (Ramesha C. Nagarwal *et al*., 2010 ; Mina Ibrahim Tadros *et al.,* 2010). The results were shown in Table: 6A, 6B & Figure: 8.

(b) Effect of hydrophilic and hydrophobic polymers on swelling index:

The percentage swelling index of formulations (F2-F5 (HPMC K100M & EC): F7-F9 (HPMC K4M & EC): F12-F15 (HPMC K15M & EC): F17-F20 (MC & EC) containing the combination of hydrophilic and hydrophobic polymers were found to increase in the following order.

HPMC K100M & EC > HPMC K15M & EC > HPMC K4M & EC > MC & EC

It was observed that, the tablets containing combination of both hydrophilic and hydrophobic polymers having less swelling index than that of the formulations containing hydrophilic polymers alone. This could be due to the less permeability of water into the hydrophobic polymer, which minimized the swelling of the matrix tablets (Doddayya *et al*., 2011). The results were shown in Table: 6A, 6B & Figure: 8.

Among all the twenty formulations, F1(HPMC K100M) formulation showed the maximum swelling index of 81.5% at the end of 12hours, due to high viscosity and high water retention property of HPMC K100M. The viscosity of the polymer had a major influence on swelling process and matrix integrity. It was concluded that, there exists a linear relationship between swelling process and polymer viscosity (Margret Chandira R *et al*., 2010; Deshbhratar R. M. *et al*., 2010; Praveen Kumar Mandapalli *et al*., 2012).

5. *IN VITRO* RELEASE STUDIES:

The *invitro* dissolution studies were carried out by USP type II method. The studies were performed in all the formulations for 12hours. The samples were taken at 15minutes interval for the first 1hour and 30minutes interval for the next 11hours. The absorbance was measured at 204nm by UV spectrophotometer.

(a) Effect of hydrophilic polymers on invitro drug release studies:

The *invitro* release studies of formulations (F1-HPMC K100M (80%), F6-HPMC K4M (80%), F11-HPMC K15M (80%) & F16-Methylcellulose (75%) containing hydrophilic polymers showed drug release at 75.3%, 85.6%, 80.6%, & 90.3% in 12hours respectively.

The drug release retarded in the following order,

HPMC K100M > HPMC K15M > HPMC K4M > MC

From the above results, the formulation F1 showed more retardant effect than the other formulations F6, F11, F16. This was due to the high viscosity of the polymer (HPMC K100M) than the others. The high viscosity grades induce the formation of strong viscous gel layer when they come in contact with the aqueous media that slowed down the rate of diffusion of medium into the tablet, which may results in the retardation or decrease the drug release. (Anilkumar J. Shinde *et al*., 2010; Margret Chandira R *et al*., 2010; Amit Kumar Nayak *et al*., 2011; Ramesh C. Nagarwal *et al*., 2010). The results were shown in Table: 7A, 7B, 7C, 7D & Figure: 9.

(b) Effect of hydrophilic and hydrophobic polymers on invitro drug release studies:

To increase the release retardation of the drug, the formulations were prepared by a combination of both hydrophilic and hydrophobic polymers.

In vitro release studies of formulations containing combination of both hydrophilic and hydrophobic polymers. The results were shown in Table: 7A, 7B, 7C, 7D & Figure: 10, 11, 12 & 13.

The cumulative % drug release of formulations containing F2 (HPMC K100M 75% & EC 5%)**;** F7 (HPMC K4M 75% & EC 5%)**;** F12 (HPMC K15M 75% & EC 5%)**;** F17 (MC 70% & EC 5%) showed 74.5%, 84%, 79.6%, & 89.7% in 12 hours respectively.

The cumulative % drug release of formulations containing F3 (HPMC K100M 70% & EC 10%)**;** F8 (HPMC K4M 70% & EC 10%)**;** F13 (HPMC K15M 70% &

EC 10%); F18 (MC 65% & EC 10%) showed 73.3%, 83.6%, 78.6%, & 88% in 12 hours respectively.

The cumulative % drug release of formulations containing F4 (HPMC K100M 65% & EC 15%); F9 (HPMC K4M 65% & EC 15%); F14 (HPMC K15M 65% & EC 15%); F19 (MC 60% & EC 15%) showed 71.3%, 82.5%, 77.7%, & 87.8% in 12 hours respectively.

The cumulative % drug release of formulations containing F5 (HPMC K100M 60% & EC 20%); F10 (HPMC K4M 60% & EC 20%); F15 (HPMC K15M 60% & EC 20%); F20 (MC 55% & EC 20%) showed 67.1%, 81.3%, 76.6%, & 86.7% in 12 hours respectively.

The drug release retarded in the following order,

HPMC K100M & EC > HPMC K15M & EC > HPMC K4M & EC > MC & EC

From the above results, it was observed that the drug release was slower for formulations containing F2 – F5, F7 – F10, F12 – F15, F17 – F20 due to the decreased concentration of hydrophilic polymer and increased concentration of hydrophobic polymer. Ethyl cellulose is hydrophobic in nature, which restricts the penetration of dissolution medium inside the matrix and also restricts the formation of gel layer around the matrix. So that, the drug release from the hydrophobic matrix decreased as compared to the hydrophilic polymers. Hence, it was concluded that the floating matrix tablets prepared with combination of hydrophilic and hydrophobic polymer showed better controlled drug release than those prepared using hydrophilic polymers alone (Amit K. Jain *et al*., 2011; Deshbhratar R. M *et al*., 2010).

Among all the twenty formulations, F5 (HPMC K100M 60% & EC 20%) was selected as a best formulation which had the better retardant effect (67.1% in 12 hours).

6. *INVITRO* DRUG RELEASE KINETICS STUDIES:

To analyze the release mechanism as well as to select the formulation for *in vivo* studies, the *invitro* release data were fitted into various release equations and kinetic models (zero order, first order, Higuchi, Hixson-Crowell, Korsemeyer-Peppas). The release kinetic data for all the formulations were shown in the Table: 8A &8B & Figure: 14.

The kinetic studies of all the formulations showed that zero order plots were fairly linear as indicated by their high regression values. Therefore it was ascertained that the drug release from all the formulations followed zero order kinetics **(**Regression coefficient values (R^2) between 0.959 – 0.993) (Praveen Kumar Mandapalli *et al*., 2012). Further F5 formulation showed the closest linearity to unity (R^2 =0.993).

Diffusion is related to the transport of drug from the dosage form into the *invitro* study fluid depending on the concentration (Ravikumar *et al.,* 2009). This was explained by Higuchi's model. The release profiles of drug from all the formulations could be best expressed by Higuchi's equations (Amit Kumar Nayak *et al*., 2011), as the plot showed high linearity with regression coefficient values (R^2) between 0.949 – 0.992.

The kinetic data of all the formulations showed good fit in Korsmeyer equation which showed the combined effect of diffusion and erosion mechanism for controlled drug release. By using Korsmeyer-peppas model, if n= 0.45 it indicates Fickian diffusion controlled drug release (Mina Ibrahim Tadros *et al*., 2010), if n=0.89 it indicates swelling controlled drug release, if n values between 0.45 to 0.89 can be regarded as an indicator

for both the phenomena (Anomalous transport or Non-Fickian diffusion) (Ramesh C. Nagarwal *et al*., 2010; Amit Kumar Nayak *et al*., 2011; Praveen Kumar *et al*., 2011). It's clear that all formulations have 'n' values between 0.45 to 0.89**,** indicating Anomalous transport (Both diffusion and erosion).

It was found that the mechanism for all formulations were Anomalous Non-Fickian diffusion (the release from initially dry, hydrophilic glassy polymers that swell when added to water and become rubbery show anomalous diffusion as a result of the rearrangement of macromolecular chains) (Sasa Baumgartner *et al.,* 2000).

V. SELECTION OF BEST FORMULATION:

From above the results of characterization F5 was selected the best formulation.

- ✶ *Invitro* Release Profile ⟶ 67.1% in 12hours
- ✶ *Invitro* Release Kinetics ⟶ Zero Order Kinetics (Closest Linearity $R^2 = 0.993$)
- ✶ Floating Lag Time ⟶ Floats Immediately

A) EVALUATION OF BEST FORMULATION

The selected of best formulation were subjected to,

1. Comparison with marketed formulation
2. Assay by HPLC method
3. Scanning Electron Microscopy
4. *In vivo* x-ray studies
5. Stability studies

1. COMPARISON WITH MARKETED FORMULATION

The promising formulation (F5) as found by evaluation studies was compared with marketed product (Conventional Tablet - Valent 40mg). The cumulative % drug release of the best formulation was found to be 67.1% in 12hours when compared to the marketed product whose cumulative % drug release was 101% in 1hour. Thus the formulation F5 showed controlled release profile than the marketed conventional tablet. The results were shown in Figure: 15.

2. ASSAY BY HPLC METHOD

The percentage of valsartan content from the best formulation was determined by high performance liquid chromatography (HPLC) method and was found to be 100.573% (40.229mg of Valsartan). Hence, the percentage drug content of the best formulation complies with official specifications as per U.S.P (Limits: 90% - 110%). The same result was obtained by UV spectrometry while analyze the best formulation (F5). The results were shown in Figure: 16A, 16B & 17.

3. SCANNING ELECTRON MICROSCOPY

The surface topography, texture and morphology of fractured surface of best formulation were evaluated by using SEM. The SEM images of the tablets were taken before and after dissolution. The SEM images of the tablet showed intact surface without any perforations, channels or troughs. After dissolution the solvent front enters the matrix and moves slowly toward the centre of the tablet. The drug diffuses out of the matrix after it comes in contact with dissolution medium. The SEM images of the formulation showed a network in the swollen polymer through which the drug diffused to the surrounding medium. Hence, it was concluded that the drug was released from matrix by

diffusion mechanism (Manoj N. Gambhire *et al*., 2007). The results were shown in Figure: 18.

4. *IN VIVO* X-RAY STUDIES

The *in vivo* X-ray studies were carried out after getting clearance from Institutional Animal Ethical Committee and are performed on healthy albino rabbit. X-ray studies were conducted to find out the gastric retention of tablet. After administration of the best formulation developed by using barium sulphate, the duration of the tablet in the stomach was monitored by taking x-rays at periodic time intervals (0, 2, 4, 6, 8, 10, & 12) using x-ray machine. The tablet was clearly seen in the GIT at different positions on the upper part of stomach confirmed its *in vivo* floating behavior. Also the swelling of the tablet can be visualized from the increase in the size of tablets in the images taken at 2^{nd} hour, 4^{th} hour, 8^{th} hour, 10^{th} hour & 12^{th} hour. Gastric residence time was found to be more than 12 hours. Hence, it was concluded that the formulation could be retained in the gastric region to ensure complete drug release. The x-ray photographs were shown in Figure: 19.

5. *STABILITY* STUDIES

Optimized formulation F5 was subjected to stability studies at 40°C at 75% RH. The results showed no significant change in the physical appearance and drug content during storage. Thus it was found that the gastro retentive floating tablets of valsartan were stable under these storage conditions. The results were shown in the Table: 9

CHAPTER XII
SUMMARY AND CONCLUSION

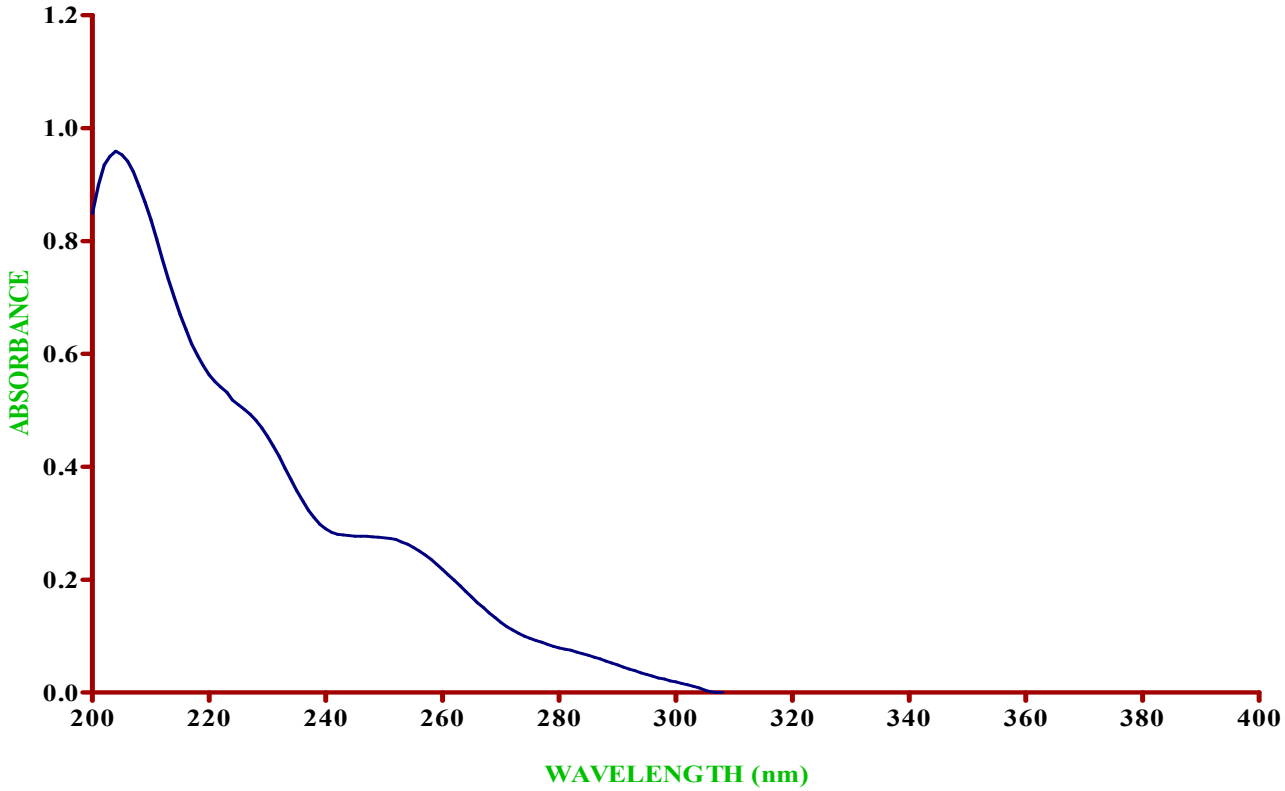
- Floating drug delivery system offers a simple and practical approach to achieve increased gastric residence time (GRT) and to modify drug release profiles essential for sustained, site specific and localized drug action.
- The present work was aimed towards developing a floating drug delivery system of valsartan based on novel approaches. It was hypothesized that a system that combines advantages of both floating and sustained release technology can be successful in the field of Novel drug delivery system.
- The floating dosage form of valsartan has been formulated to improve the absorption, by retaining the drug in stomach for a prolonged period of time.
- The λ_{max} of valsartan was found to be 204nm in 0.1N hydrochloric acid.
- The valsartan obeys the Beer's law within the concentration of 2 to 20µg/ml.
- DSC & FT-IR studies indicated that there was no interaction between drug and excipients.
- The twenty formulations of valsartan floating matrix tablets (F1-F20) were prepared by non-effervescent techniques using hydrophilic and hydrophobic polymers.
- The formulated tablets were analyzed for precompression & postcompression parameters, *invitro* release, release kinetics, *in vivo* x-ray studies, stability studies etc.
- The precompression parameters of all the formulations were within the required limit that was suitable for formulation of the tablets.

- ✶ The postcompression parameters such as hardness, friability, uniformity in weight, & drug content of all the formulated tablets were within the acceptable limits.
- ✶ The floating lag time & duration of buoyancy were found to be satisfied.
- ✶ Polymer swelling was crucial in determining the drug release rate and also important for flotation. The viscosity of the polymer had a major influence on swelling process and matrix integrity.
- ✶ Hydrophilic polymers induce the formation of strong viscous gel layer when they come in contact with the aqueous media that slowed down the rate of diffusion of medium into the tablet, which may results in the retardation or decrease the drug release.
- ✶ The combination of hydrophilic and hydrophobic polymers, which restricts the penetration of dissolution medium inside the matrix, also restricts the formation of gel layer around the matrix. So that, the drug release from the hydrophobic matrix tablets decreased as compared to the hydrophilic polymers. It was concluded that the floating matrix tablets prepared with the combination of both hydrophilic & hydrophobic polymer showed better controlled drug release than those prepared using hydrophilic polymers alone.
- ✶ The *in vitro* dissolution studies of all the formulations showed controlled release of the drug over a period of 12hrs. Among all the twenty formulations, F5 (HPMC K100M 60% & EC 20%) was selected as a best formulation which had the better retardant effect (67.1% in 12 hours) & subjected to further studies.
- ✶ All the formulations followed zero order kinetics and Anomalous Non-Fickian diffusion mechanism.

- ✶ The selected formulation showed controlled release profile than the marketed conventional tablet.
- ✶ The HPLC analysis of best formulation complies with official specifications as per U.S.P.
- ✶ The SEM images of the selected formulation showed intact surface without any perforations, channels or toughs.
- ✶ The *in vivo* x-ray studies showed that the best formulation had gastric retention time of more than 12hrs.
- ✶ The selected formulation was found to be stable under the storage conditions.

CONCLUSION

The results of the present study clearly indicate the feasibility to develop valsartan in the form of floating drug delivery system with prolongation of gastric retention time and controlled drug release. The future studies may be extended to reveal the pharmacokinetic parameters related to bioavailability and clinical trial investigations, which may prove that this type of the formulation can be administered safely for the treatment of hypertension with improved therapeutic efficacy.



λ_{max}=204nm

FIGURE 1: DETERMINATION OF λ_{max} *OF VALSARTAN*

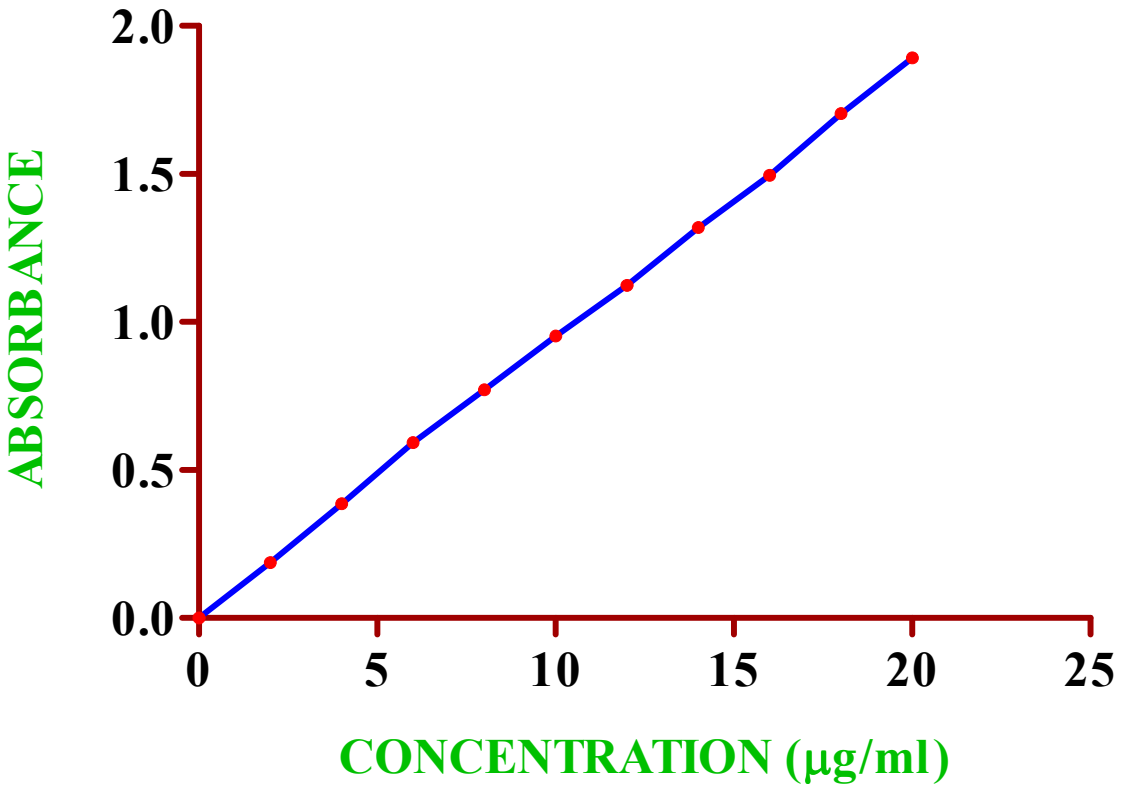
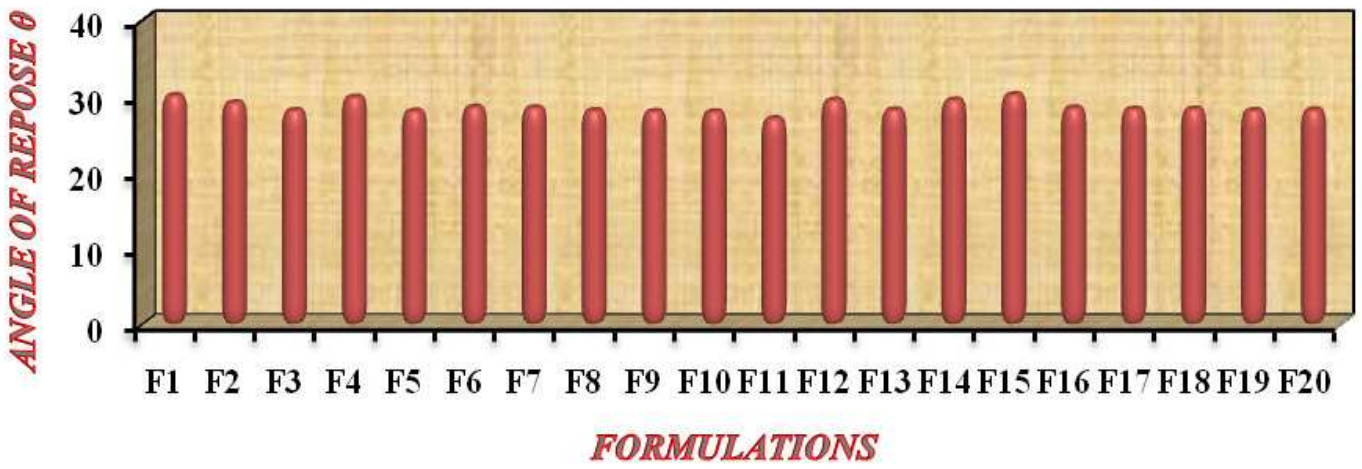
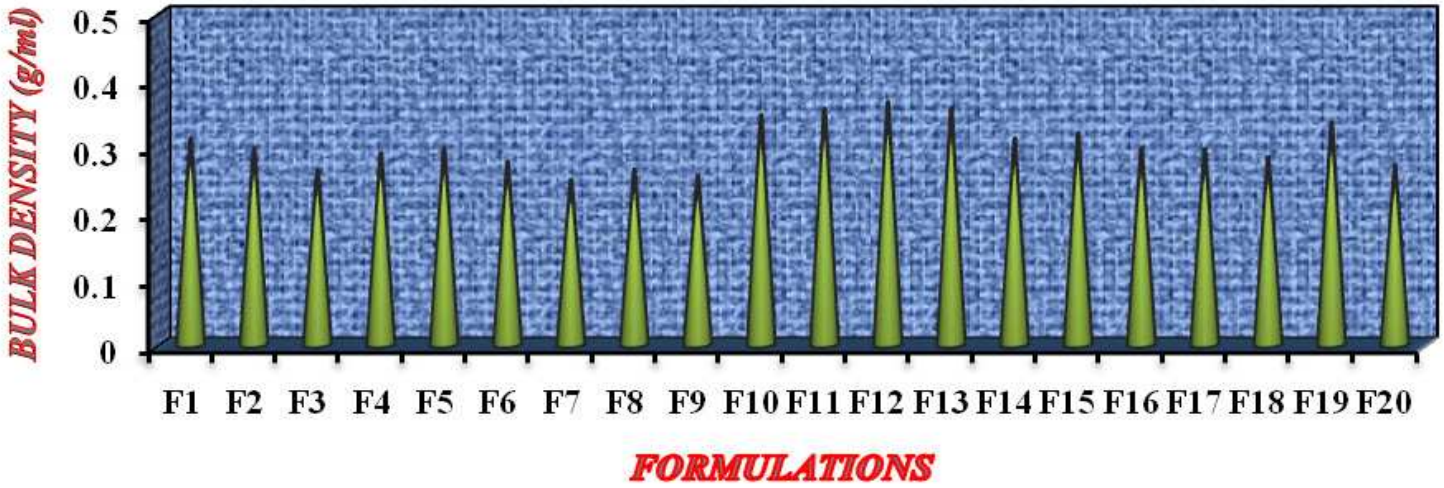


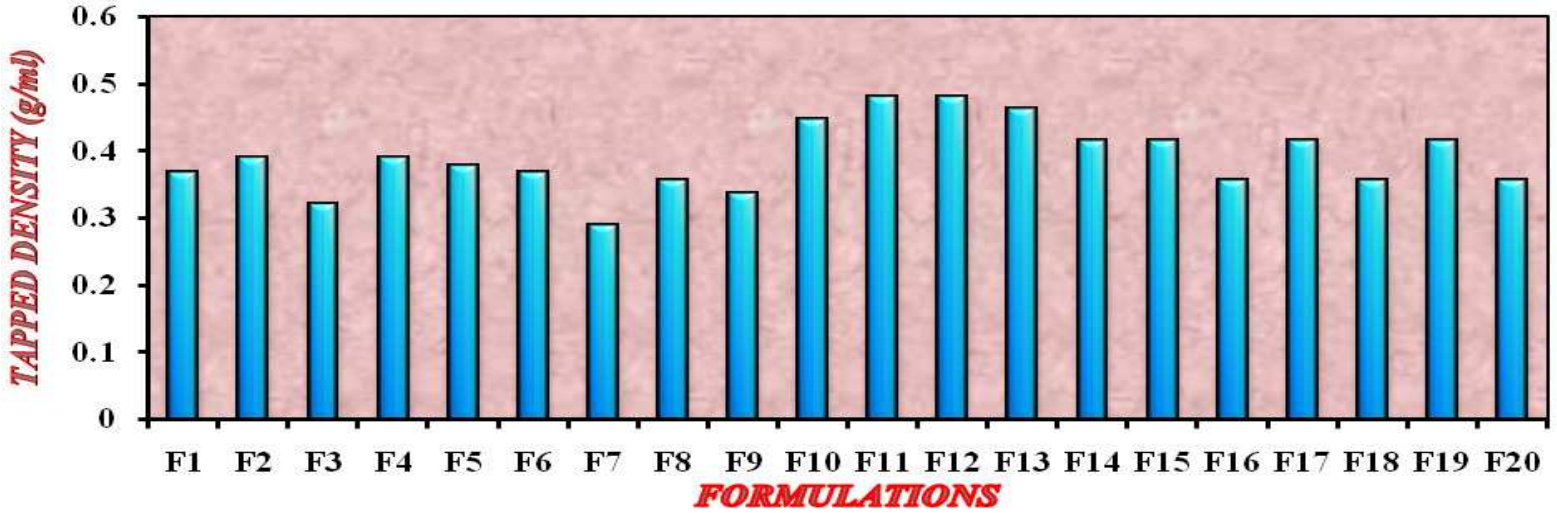
FIGURE 2: CALIBRATION CURVE OF VALSARTAN IN 0.1N HYDROCHLORIC ACID



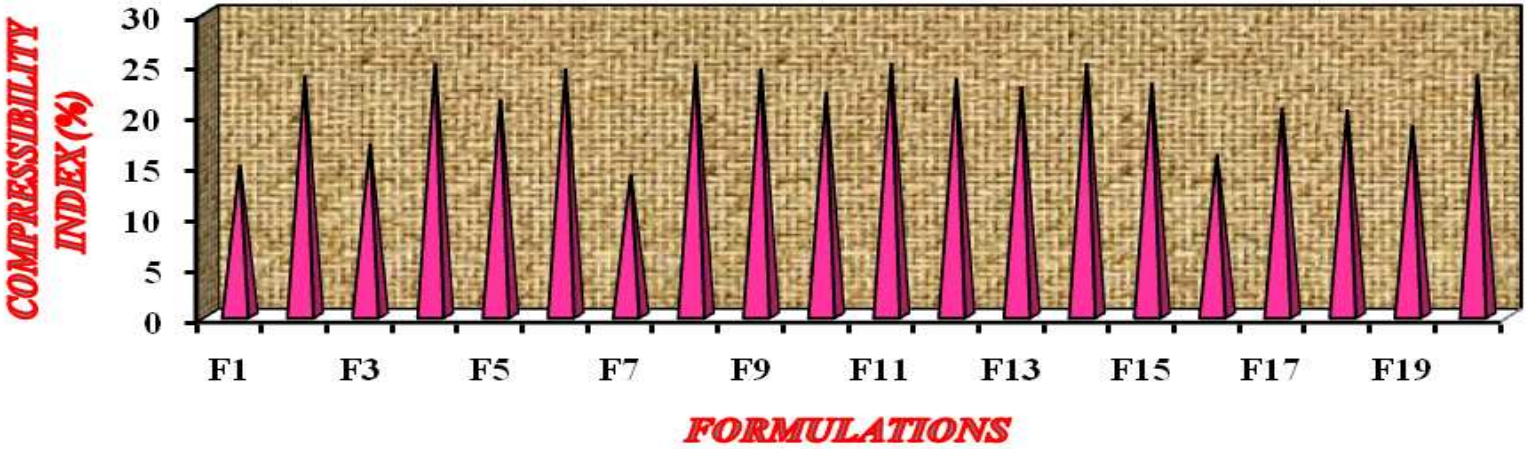
(A) ANGLE OF REPOSE OF DRUG AND POWDER BLEND



(B) BULK DENSITY OF DRUG AND POWDER BLEND

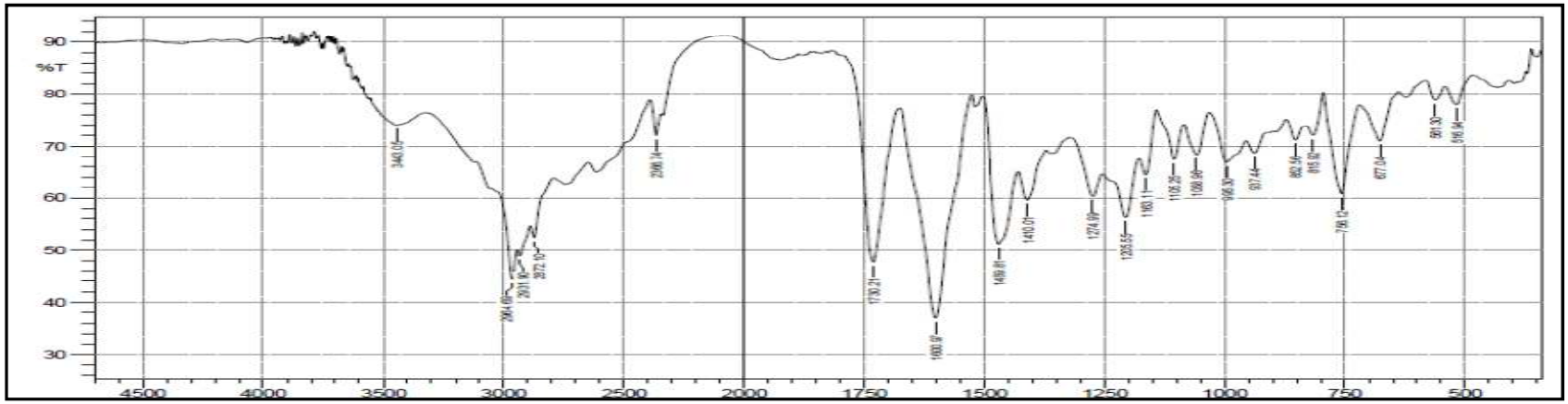


(C) TAPPED DENSITY OF DRUG AND POWDER BLEND

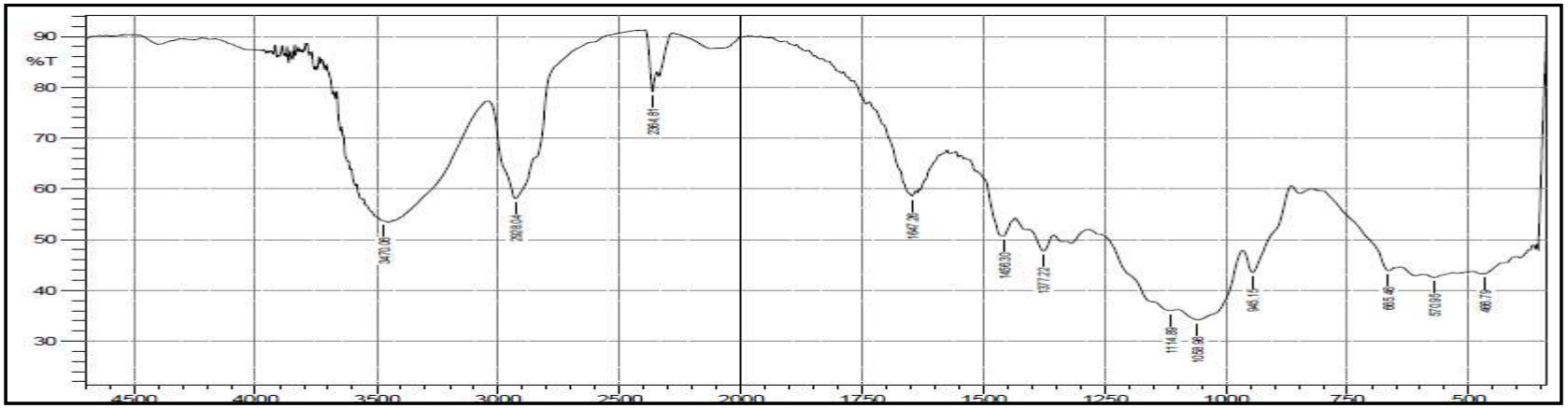


(D) COMPRESSIBILITY INDEX OF DRUG AND POWDER BLEND

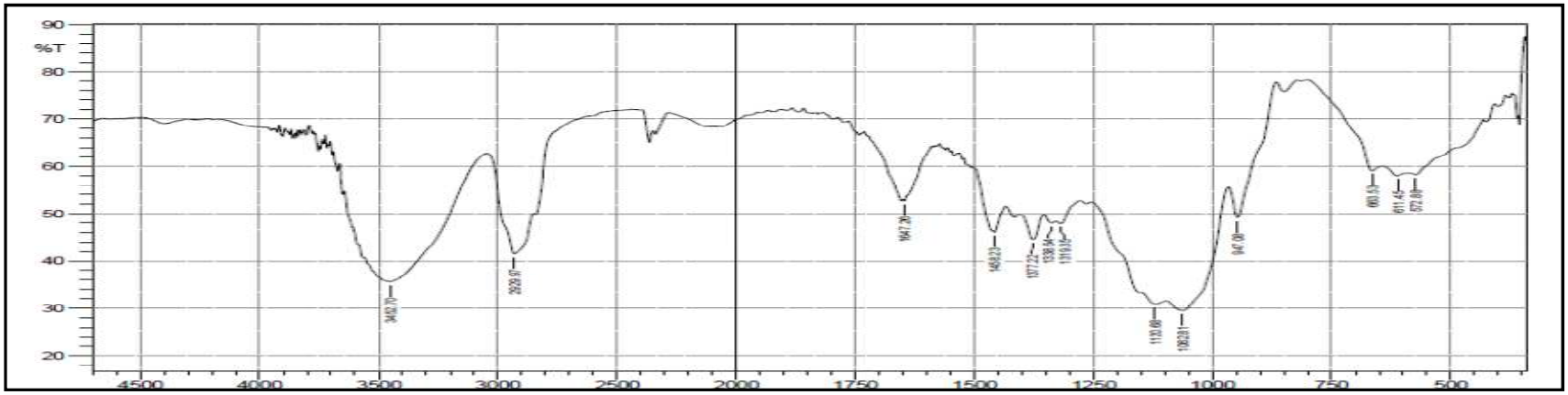
(A) FT-IR SPECTRA OF VALSARTAN



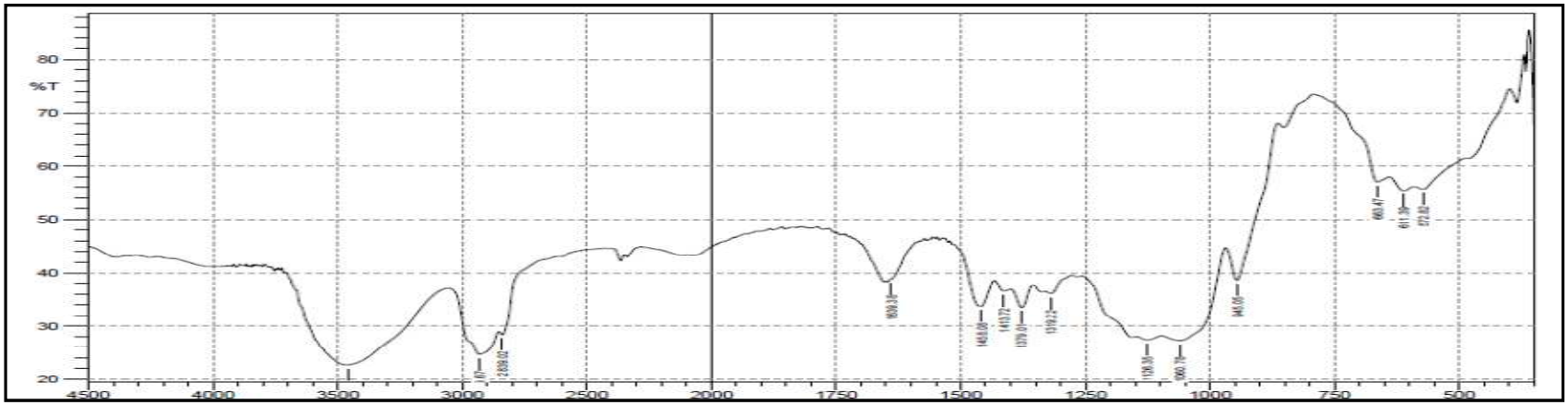
(B) FT-IR SPECTRA OF HPMC K4M



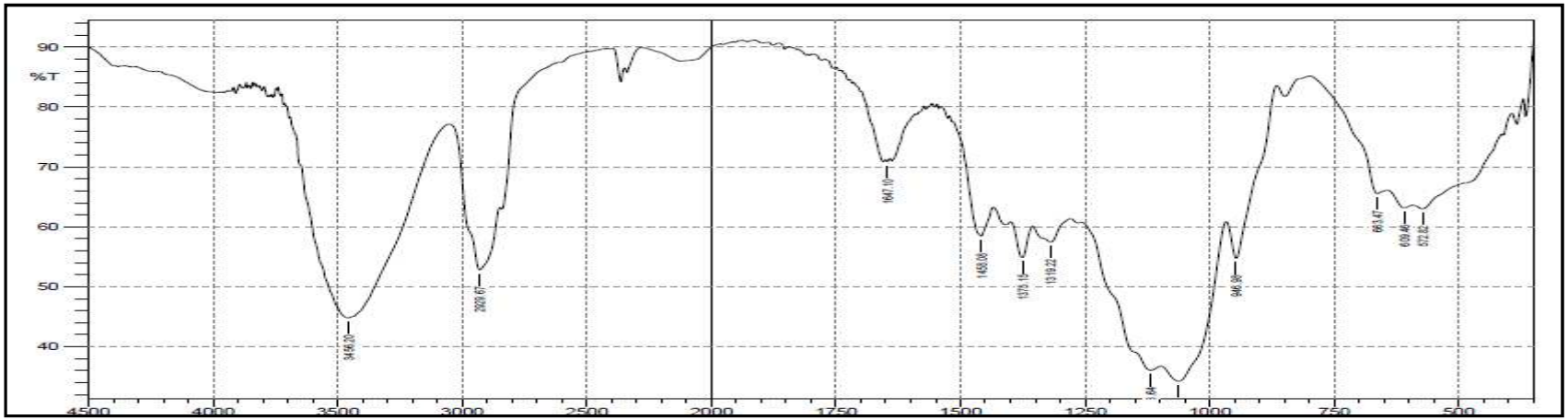
(C) FT-IR SPECTRA OF HPMC K15M



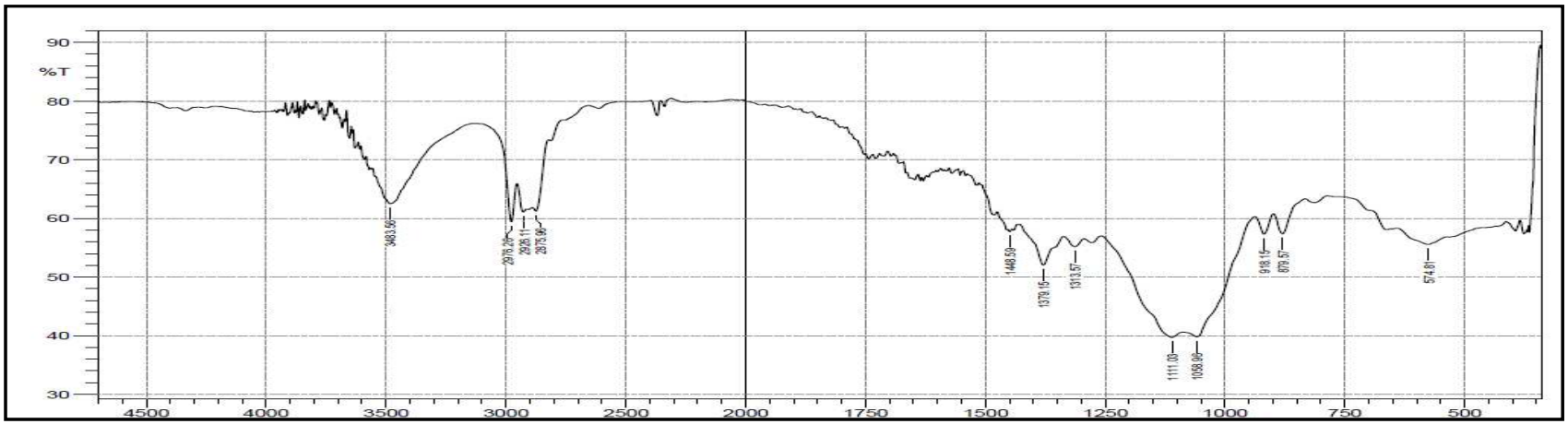
(D) FT-IR SPECTRA OF HPMC K100M



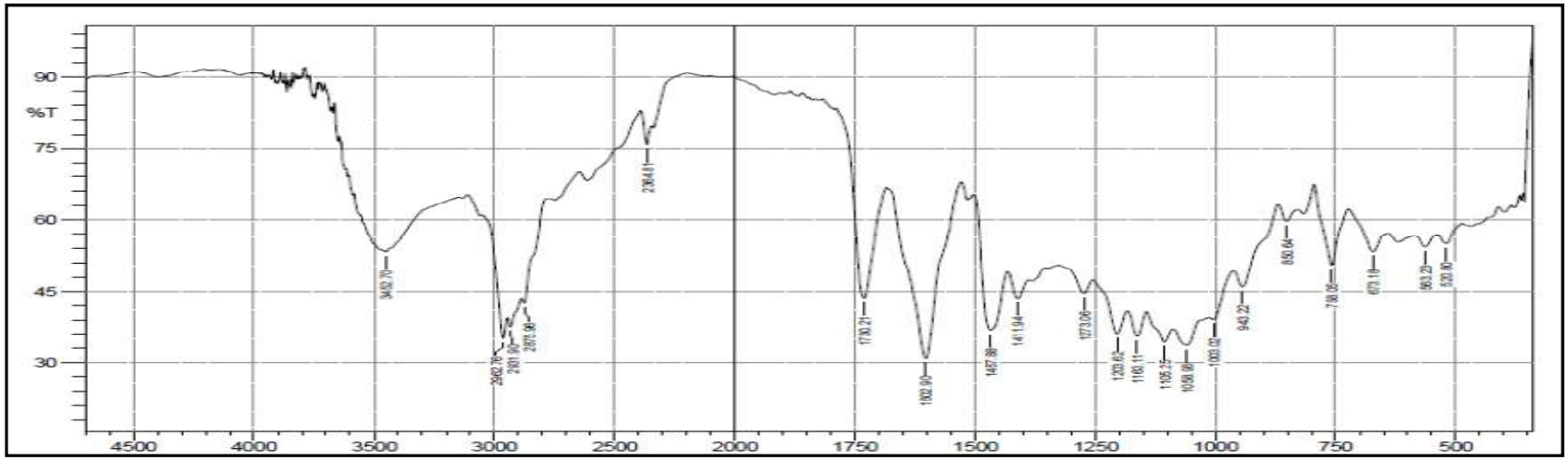
(E) FT-IR SPECTRA OF METHYLCELLULOSE



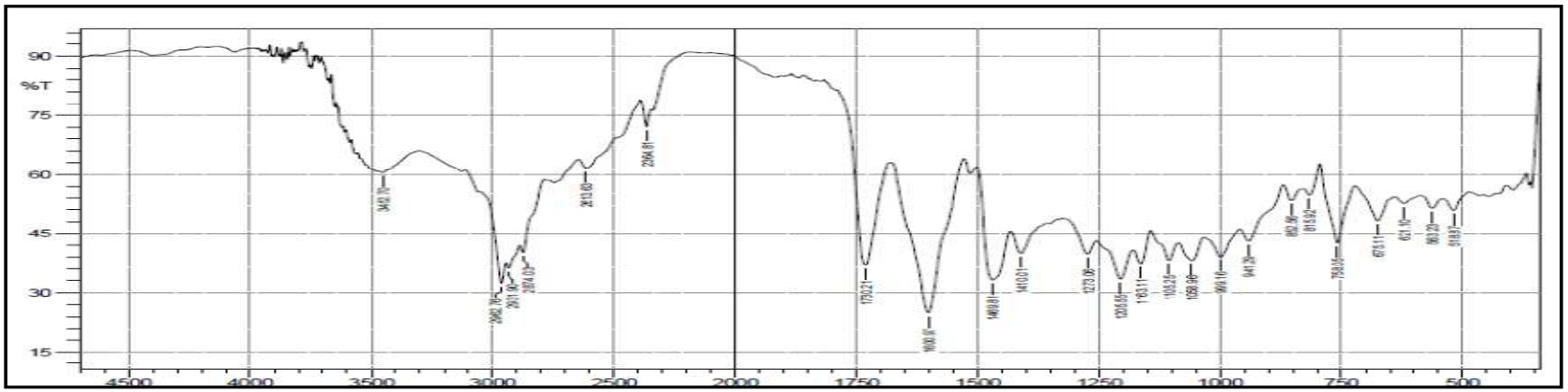
(F) FT-IR SPECTRA OF ETHYLCELLULOSE



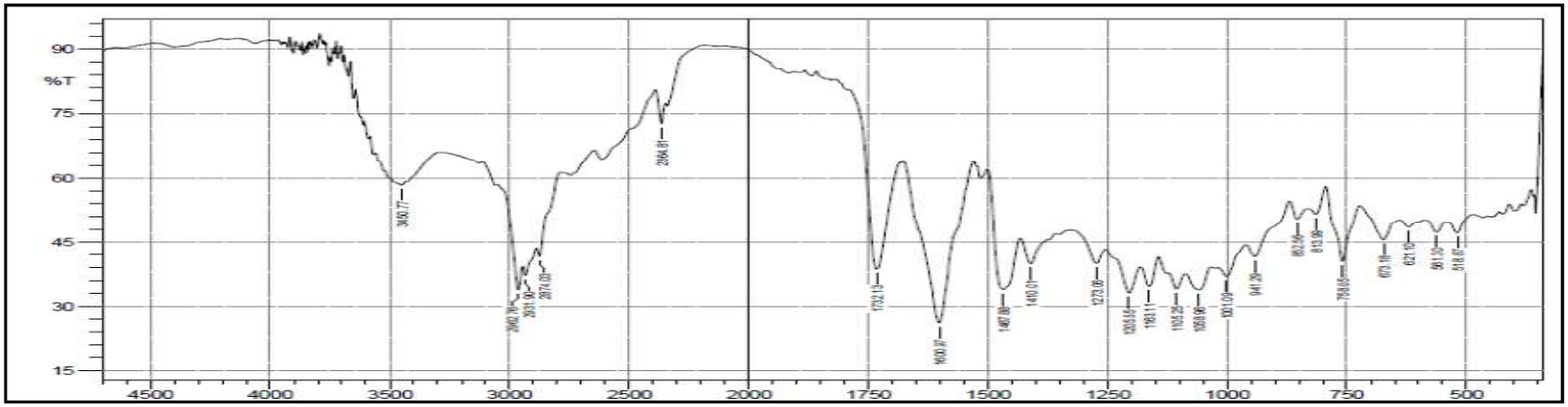
(G) FT-IR SPECTRA OF DRUG AND HPMC K15M



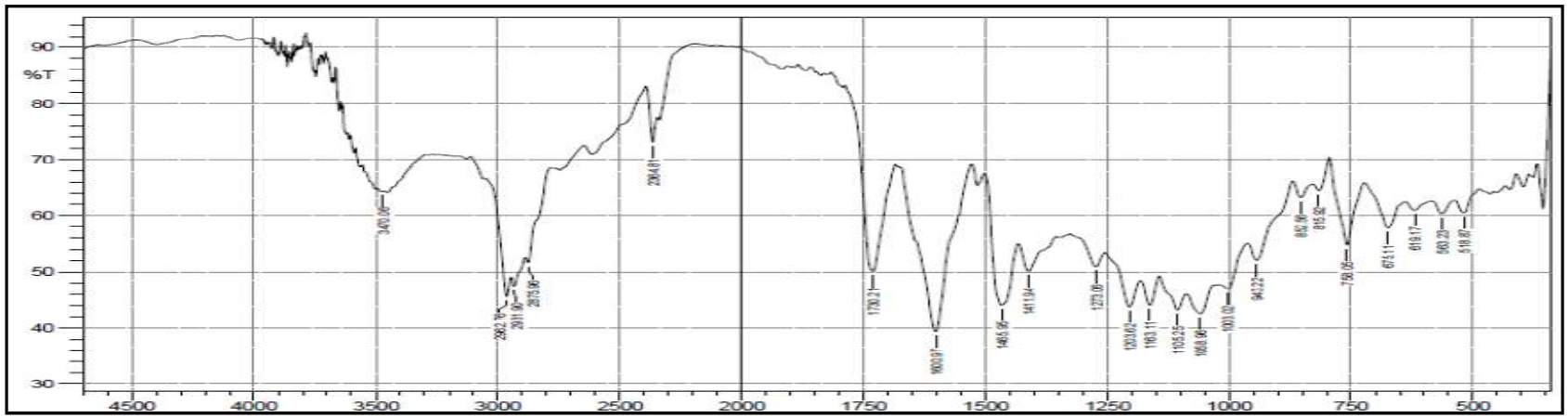
(H) FT-IR SPECTRA OF DRUG AND HPMC K4M



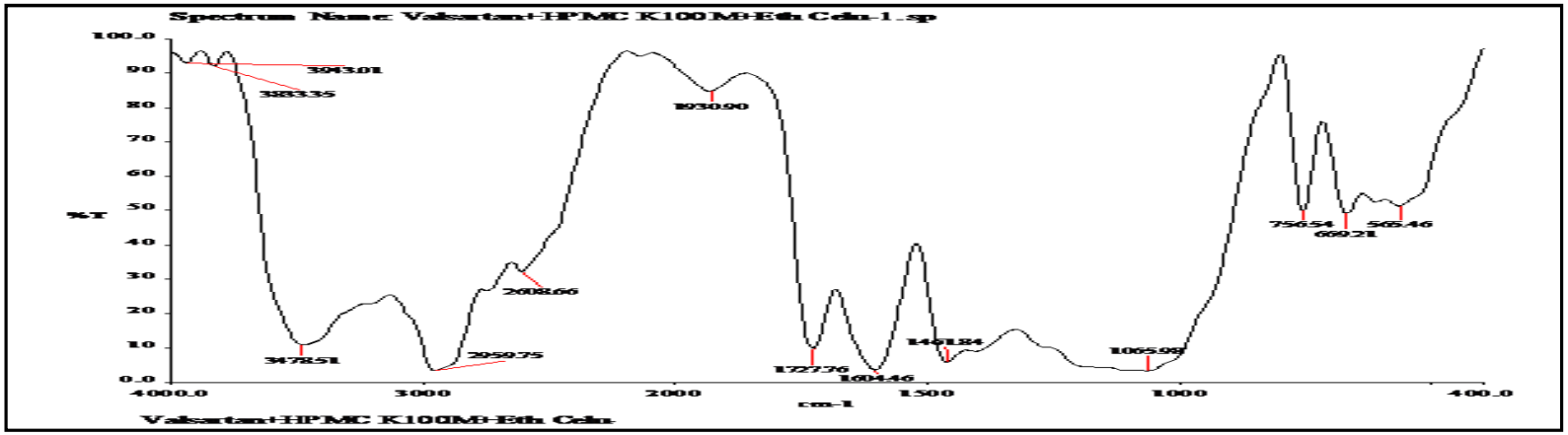
(I) FT-IR SPECTRA OF DRUG AND HPMC K100M



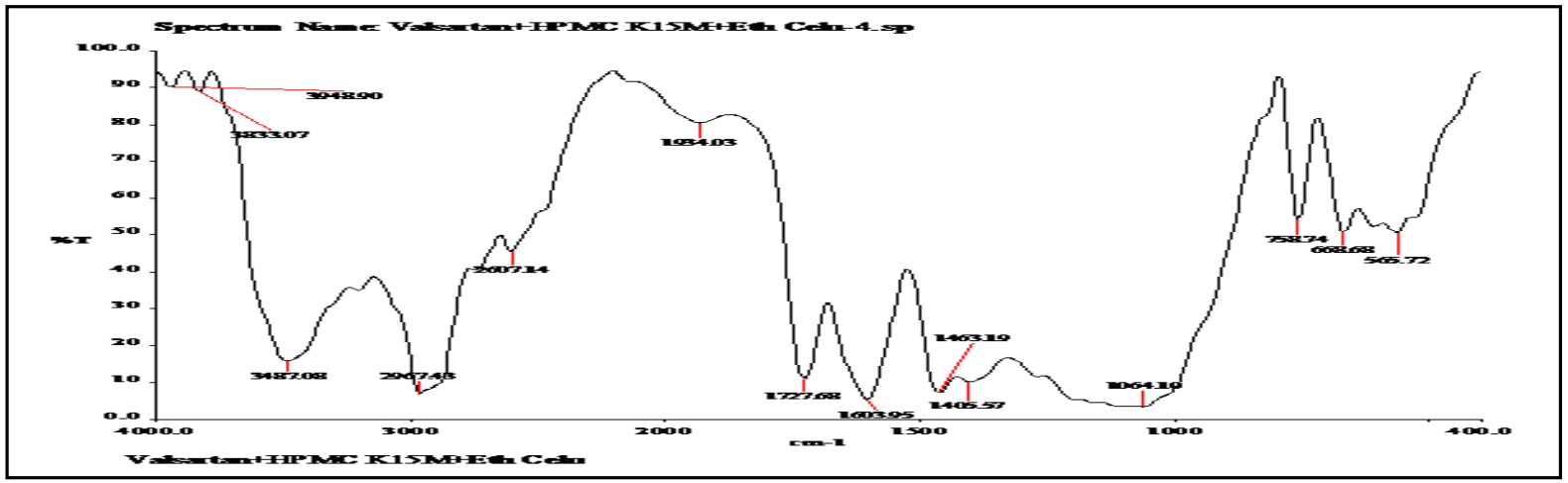
(J) FT-IR SPECTRA OF DRUG AND MC



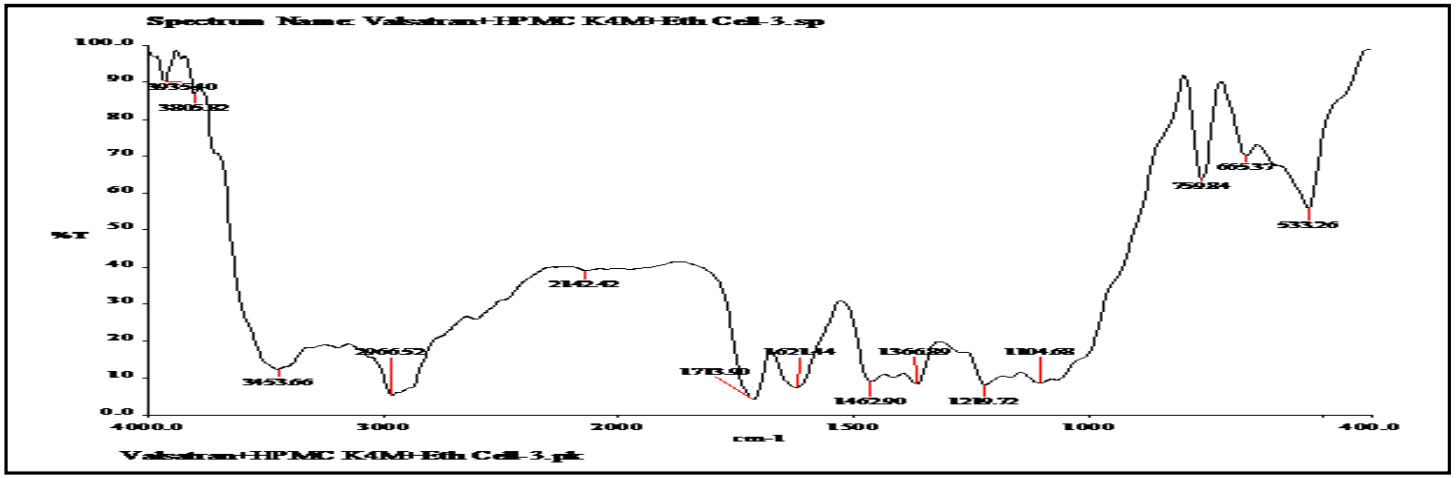
(K) FT-IR SPECTRA OF DRUG, HPMC K100M & EC



(L) FT-IR SPECTRA OF DRUG, HPMC K15M & EC



(M) FT-IR SPECTRA OF DRUG, HPMC K4M & EC



(N) FT-IR SPECTRA OF DRUG, MC & EC

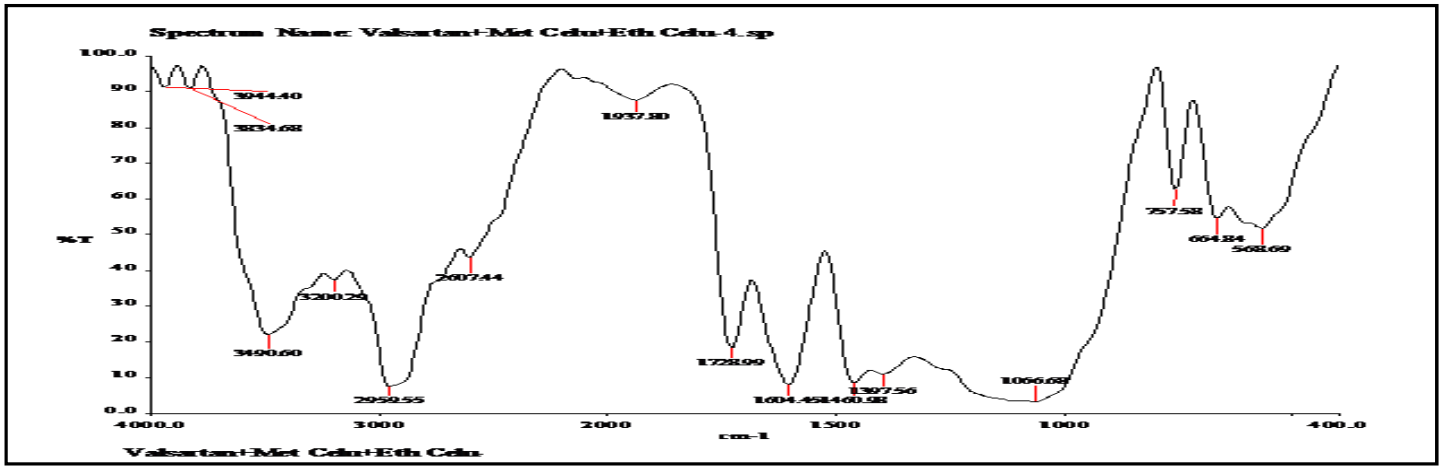
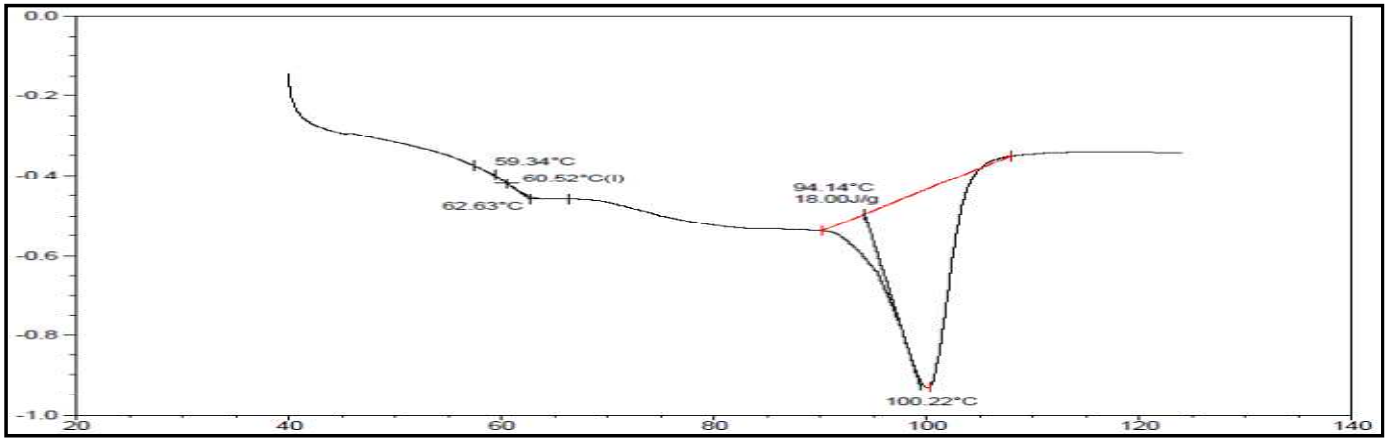
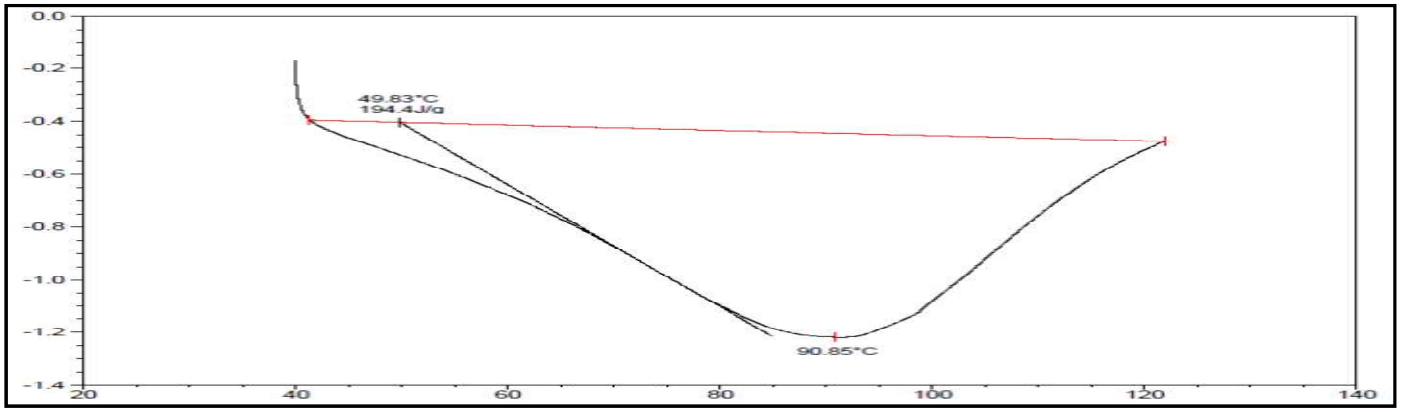


FIGURE 4: FT-IR SPECTRUM OF DRUG, POLYMERS & PHYSICAL MIXTURE

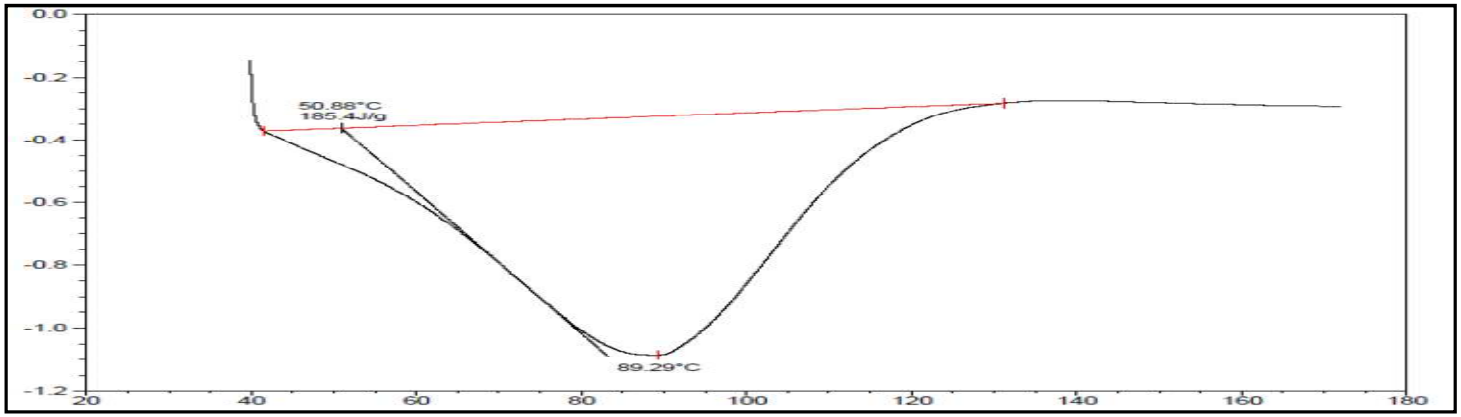
(A) DSC THERMOGRAM OF VALSARTAN



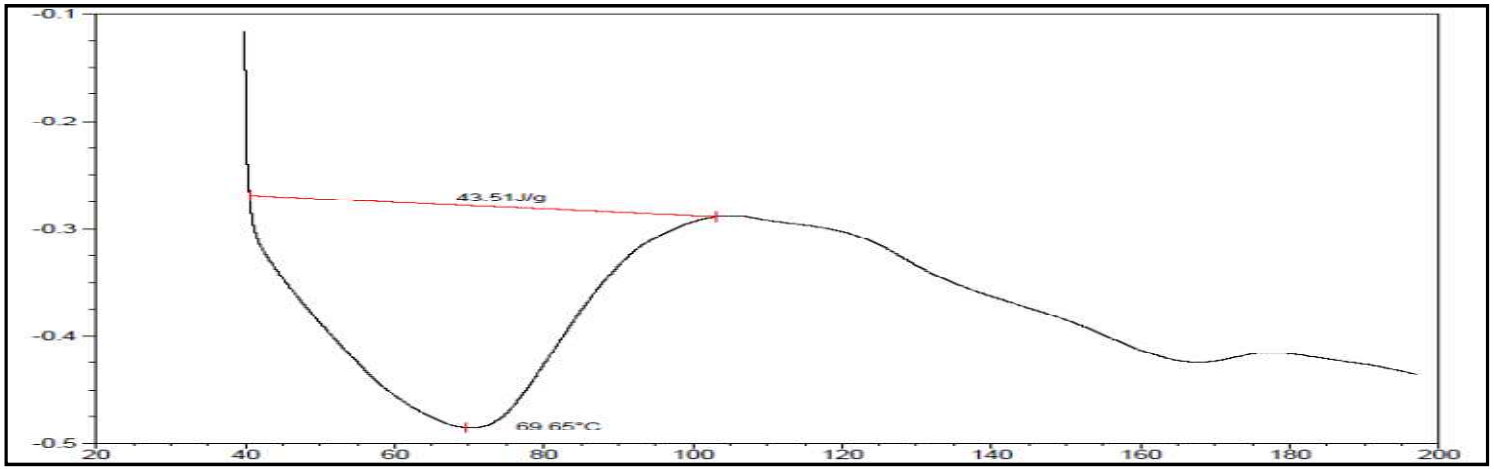
(B) DSC THERMOGRAM OF HPMC K4M



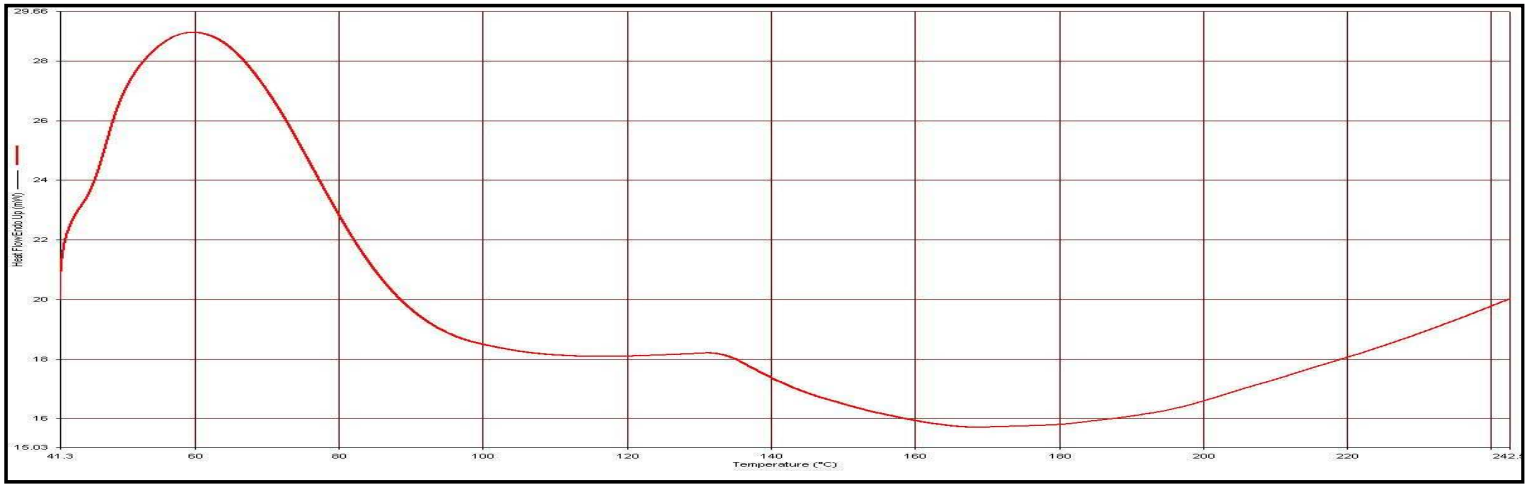
(C) DSC THERMOGRAM OF HPMC K15M



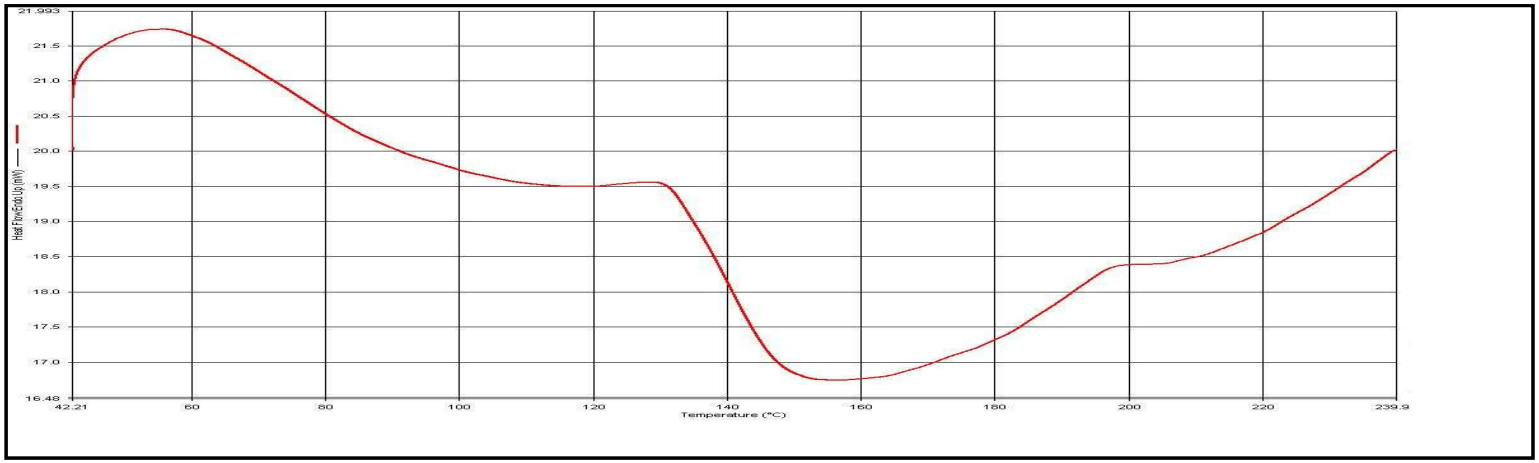
(D) DSC THERMOGRAM OF ETHYLCELLULOSE



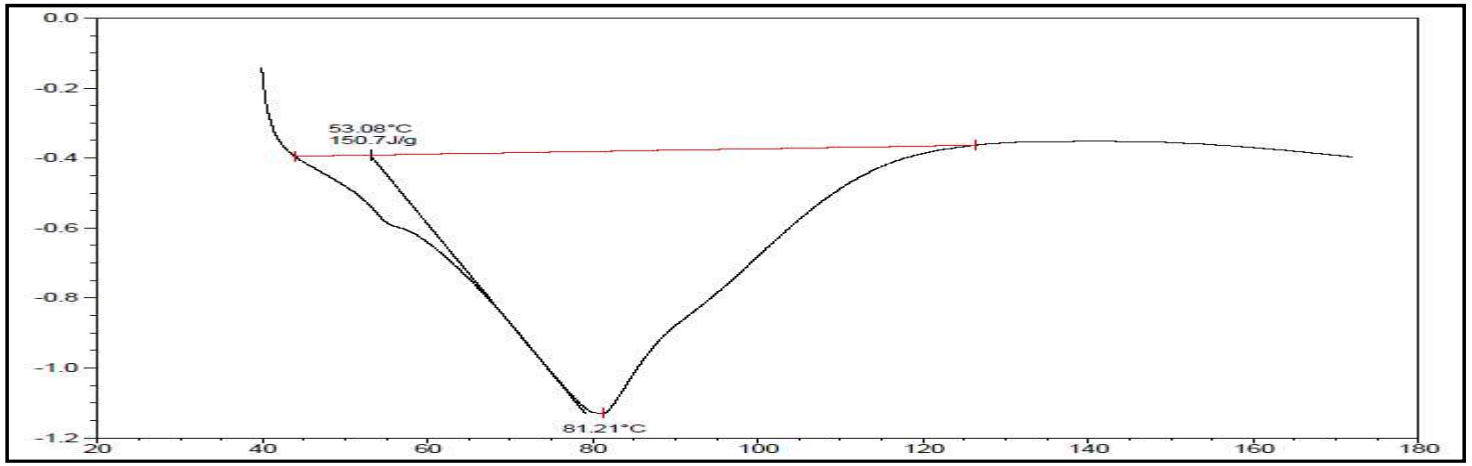
(E) DSC THERMOGRAM OF HPMC K100M



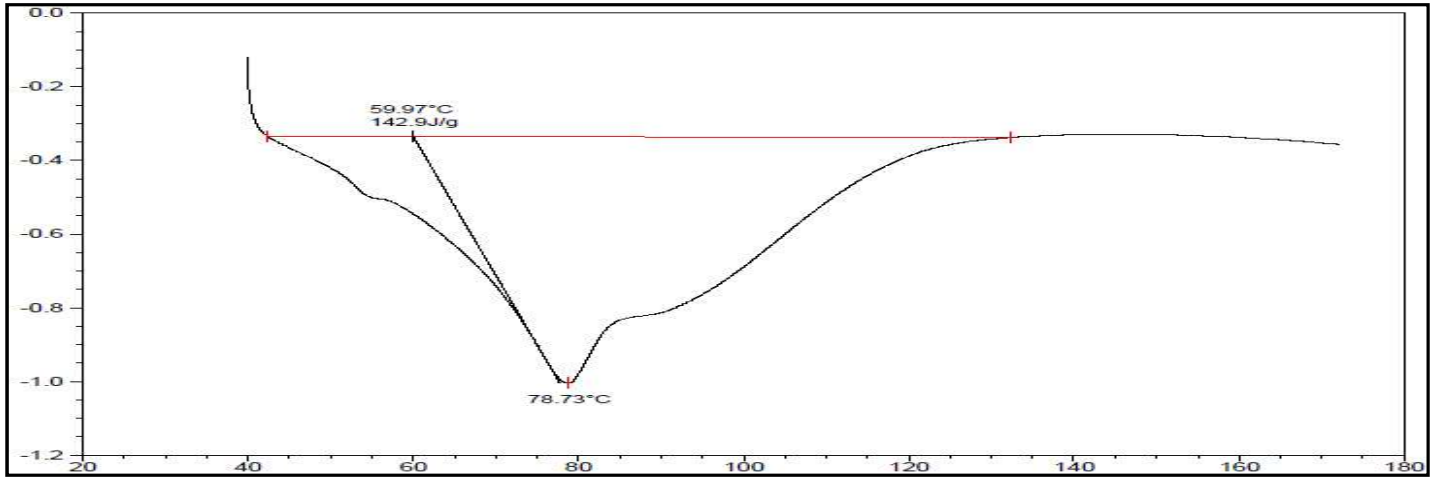
(F) DSC THERMOGRAM OF METHYLCELLULOSE



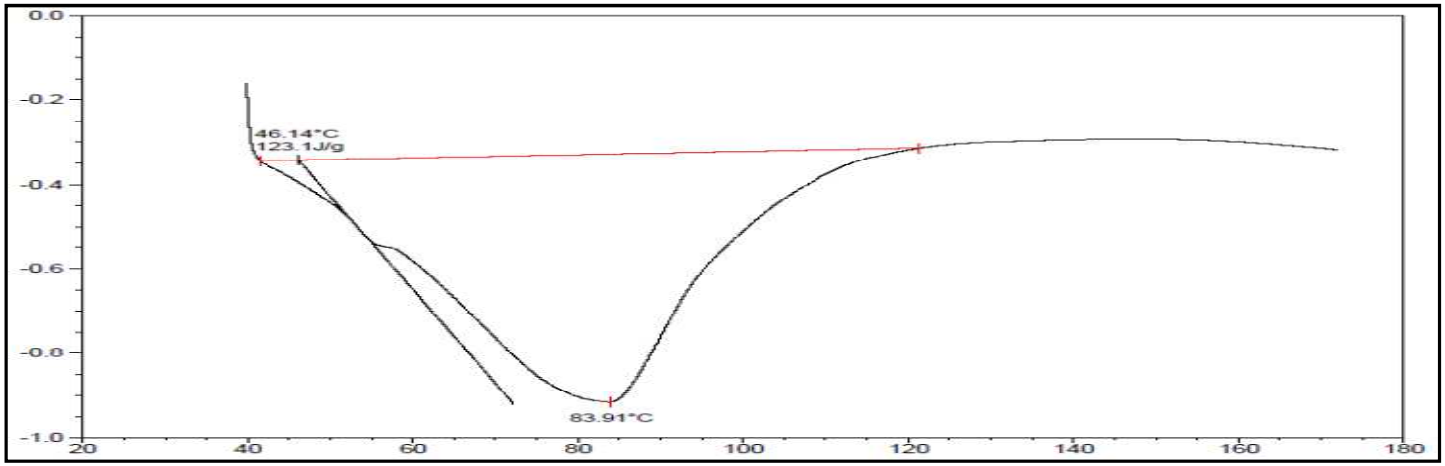
(G) DSC THERMOGRAM OF DRUG AND HPMC K100M



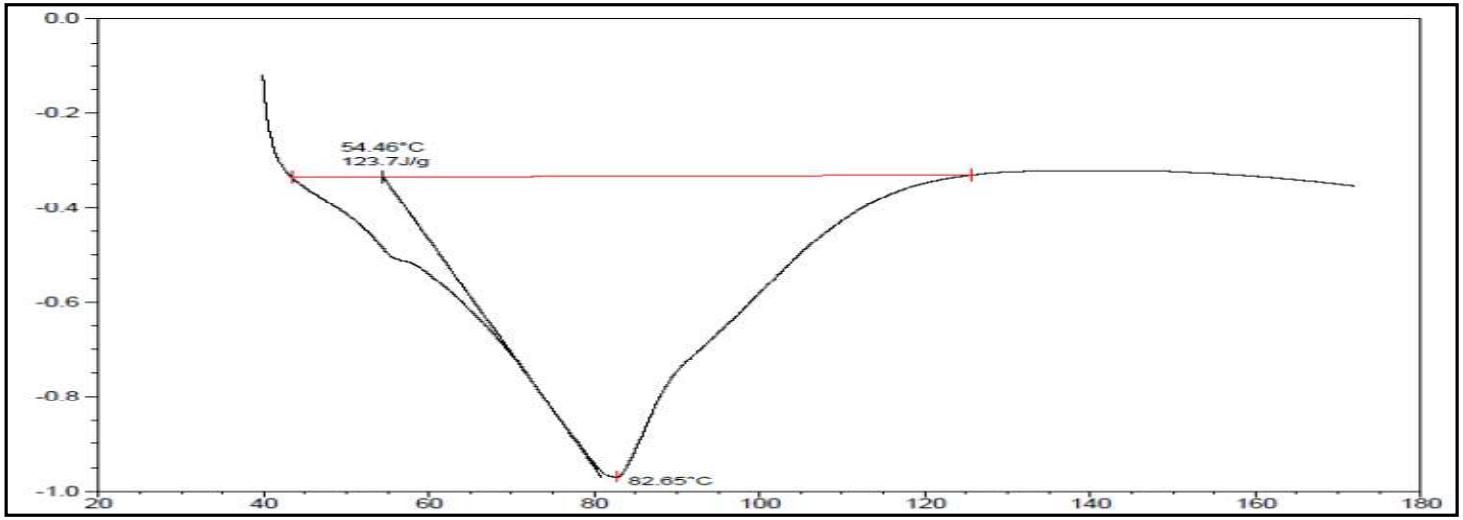
(H) DSC THERMOGRAM OF DRUG AND HPMC K4M



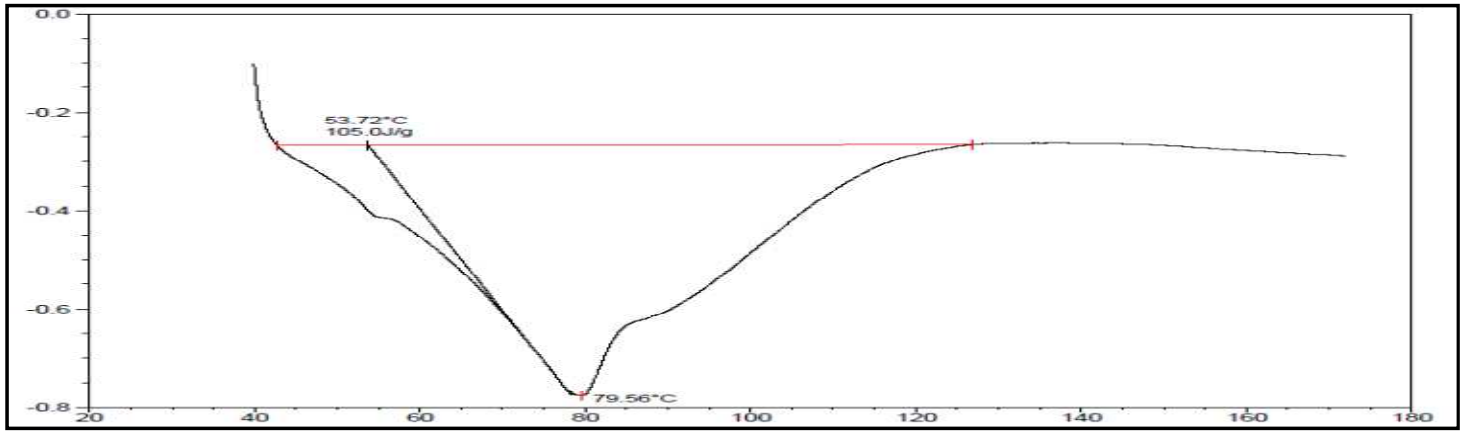
(I) DSC THERMOGRAM OF DRUG AND HPMC K15M



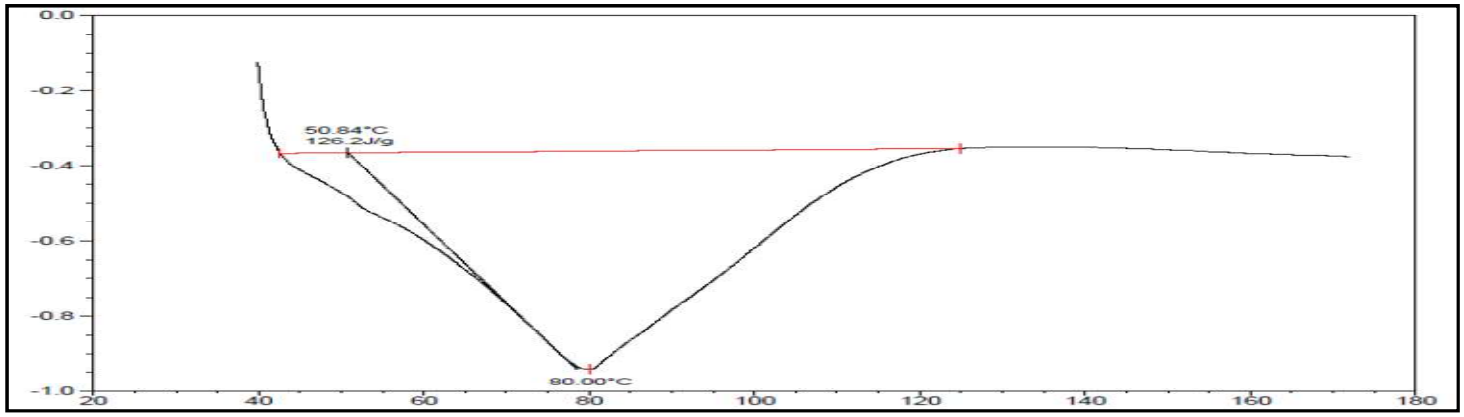
(J) DSC THERMOGRAM OF DRUG AND METHYLCELLULOSE



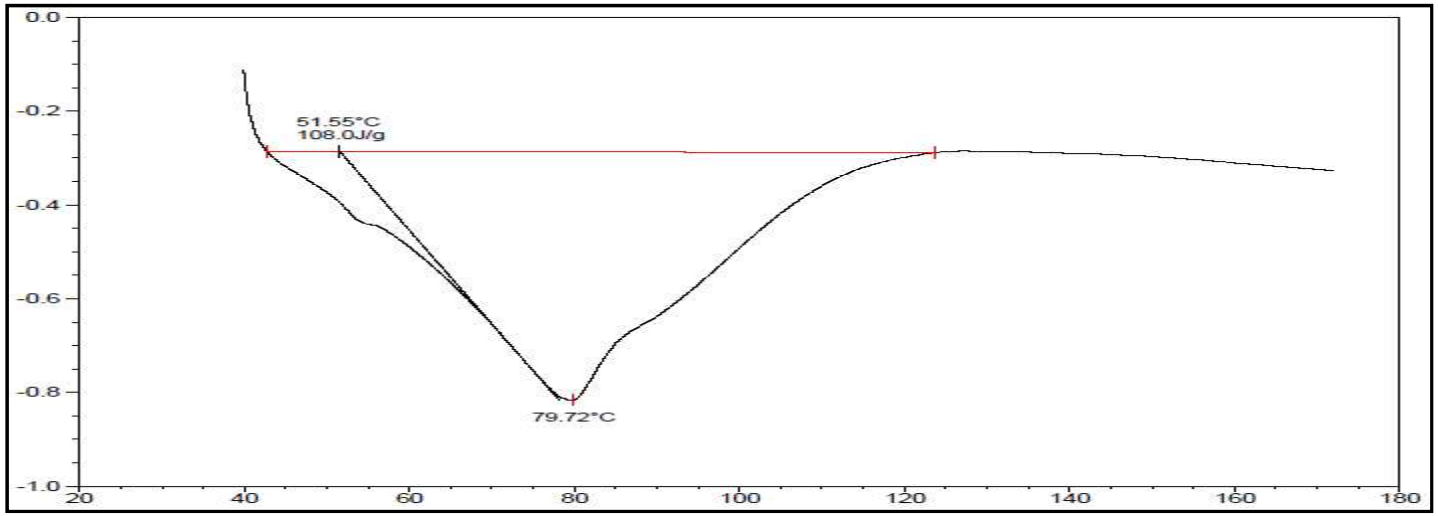
(K) DSC THERMOGRAM OF DRUG, HPMC K100M AND EC



(L) DSC THERMOGRAM OF DRUG, HPMC K4M AND EC



(M) DSC THERMOGRAM OF DRUG, HPMC K15M AND EC



(N) DSC THERMOGRAM OF DRUG, METHYLCELLULOSE AND EC

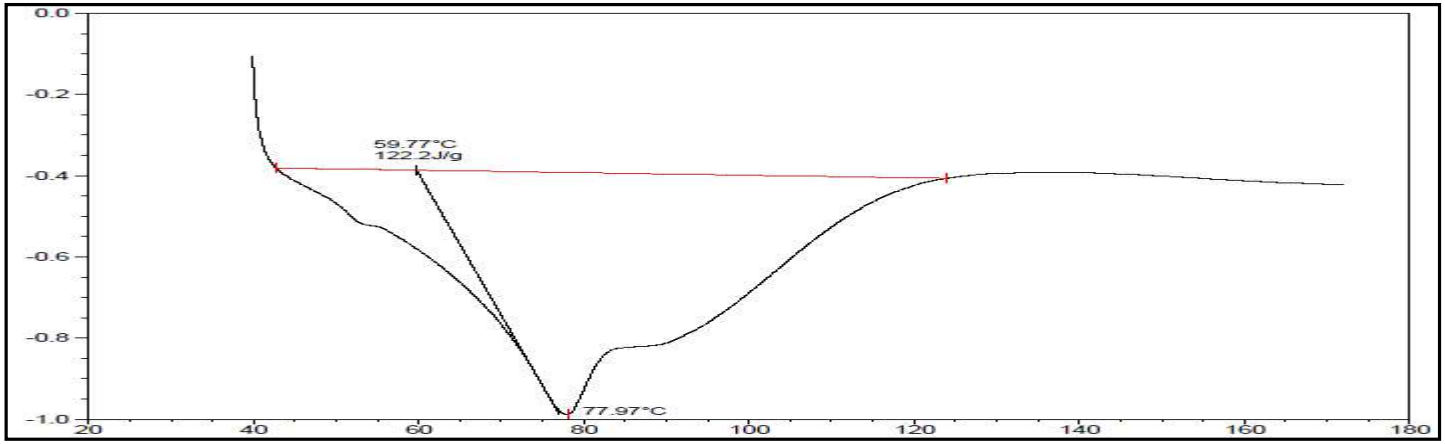
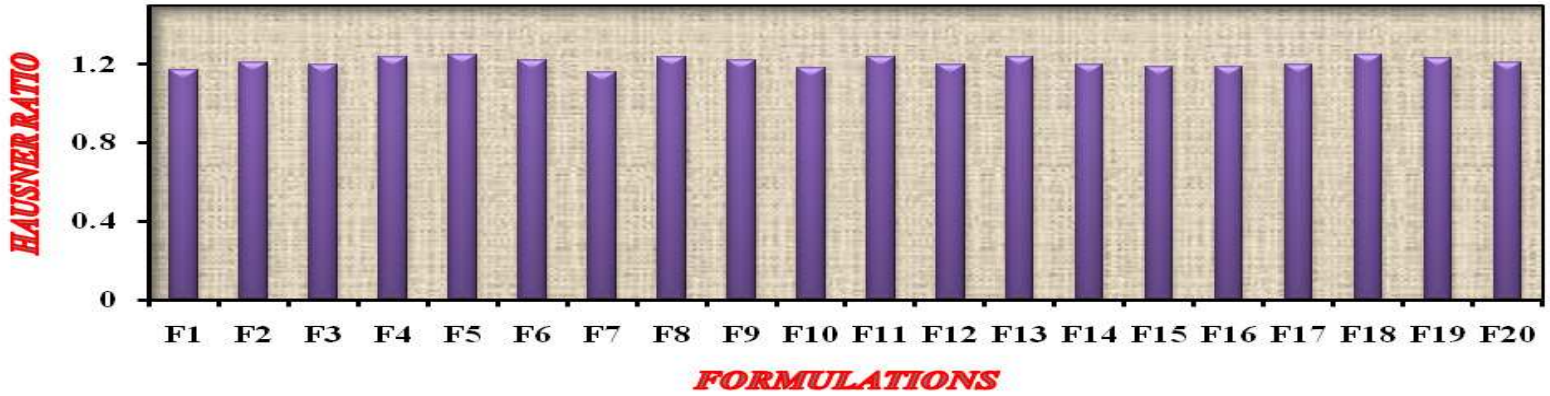
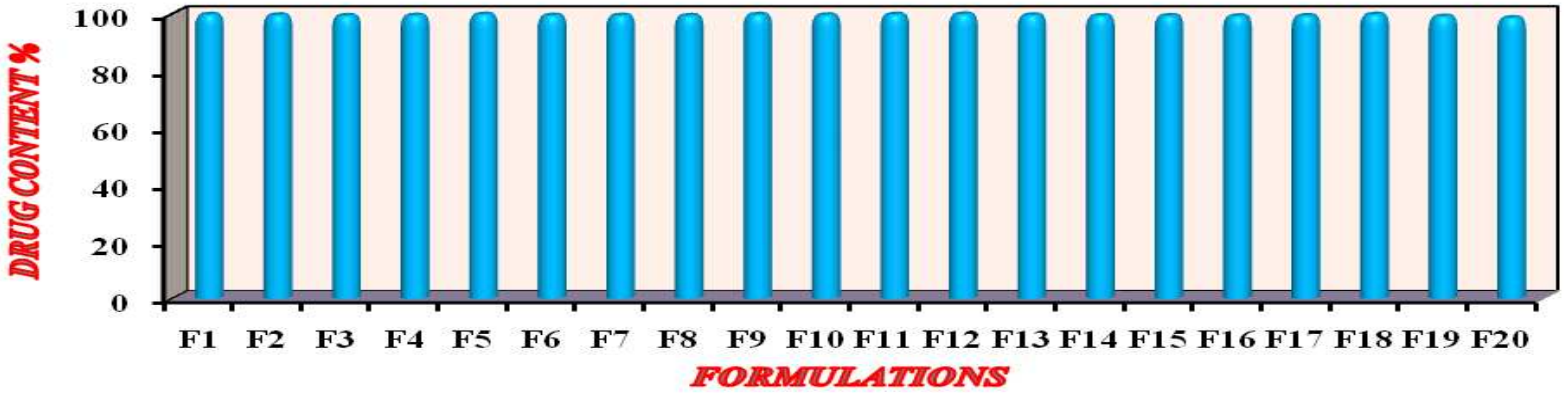


FIGURE 3: DSC THERMOGRAM OF DRUG, POLYMERS & PHYSICAL MIXTURE



(E)HAUSNER'S RATIO OF DRUG AND POWDER BLEND



(F) DRUG CONTENT OF TABLETS

FIGURE 5: (A) ***ANGLE OF REPOSE, (B) BULK DENSITY, (C) TAPPED DENSITY, (D) COMPRESSIBILITY INDEX, (E) HAUSNER'S RATIO, (F) DRUG CONTENT OF TABLETS***

(A)

(B)

(C)

(D)

(A) F1- HPMC K100M (80%); F2- HPMC K100M 75% + EC 5%; F3- HPMC K100M 70% + EC 10%.

(B) F4- HPMC K100M 65% + EC 15%; F5- HPMC K100M 60% + EC 20%.

(C) F6- HPMC K4M (80%); F7- HPMC K4M 75% + EC 5%; F8- HPMC K4M 70% + EC 10%.

(D) F9- HPMC K4M 65% + EC 15%; F10- HPMC K4M 60%+EC 20%.

(E)

(F)

(G)

(H)

(E) F11- HPMC K15M (80%); F12- HPMC K15M 75% + EC 5%; F13- HPMC K15M 70% + EC 10%.

(F) F14- HPMC K15M 65% + EC 15%; F15- HPMC K15M 60% + EC 20%.

(G) F16- MC (75%); F17- MC 70% + EC 5%; F18- MC 65% + EC 10%.

(H) F19- MC 60% + EC 15%; F20- MC 55%+EC 20%.

FIGURE 6: *IN VITRO* FLOATING BEHAVIOUR OF ALL FORMULATIONS

(A)

(B)

(C)

(D)

(A) F1- HPMC K100M (80%); F2- HPMC K100M 75% + EC 5%; F3- HPMC K100M 70% + EC 10%.

(B) F4- HPMC K100M 65% + EC 15%; F5- HPMC K100M 60% + EC 20%.

(C) F6- HPMC K4M (80%); F7- HPMC K4M 75% + EC 5%; F8- HPMC K4M 70% + EC 10%.

(D) F9- HPMC K4M 65% + EC 15%; F10- HPMC K4M 60%+EC 20%.

(E)

(F)

(G)

(H)

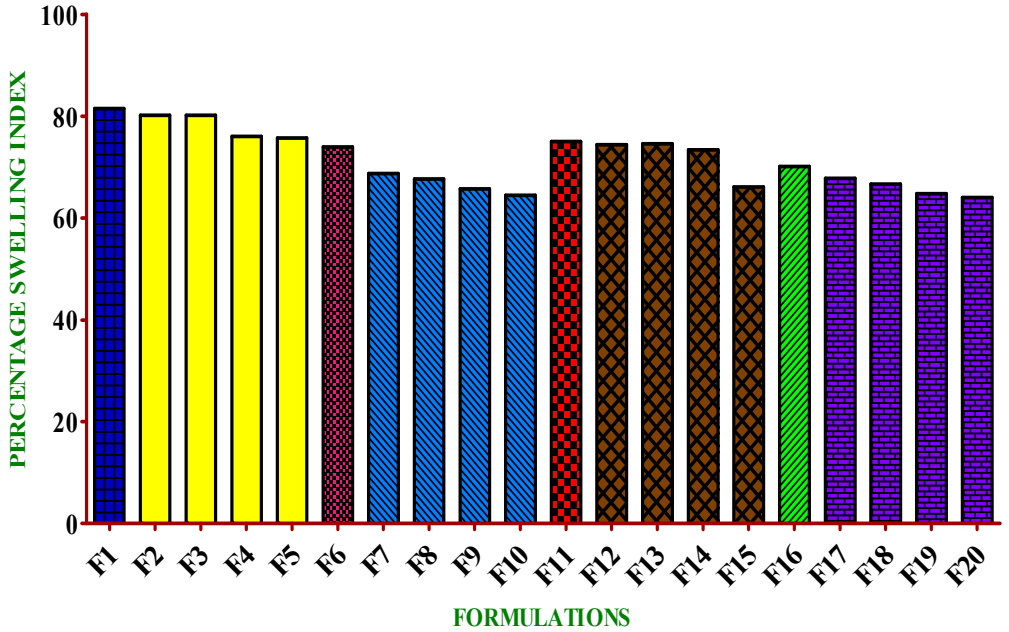
(E) F11- HPMC K15M (80%); F12- HPMC K15M 75% + EC 5%; F13- HPMC K15M 70% + EC 10%.

(F) F14- HPMC K15M 65% + EC 15%; F15- HPMC K15M 60% + EC 20%.

(G) F16- MC (75%); F17- MC 70% + EC 5%; F18- MC 65% + EC 10%.

(H) F19- MC 60% + EC 15%; F20- MC 55%+EC 20%.

FIGURE 7: SWELLING INDEX OF ALL FORMULATIONS



(F1)HPMC K100M 80%

(F2)HPMC K100M 75% & EC 5%

(F3)HPMC K100M 70% & EC 10%

(F4) HPMC K100M 65% & EC 15%

(F5) HPMCK100M 60% & EC 20%

(F6) HPMC K4M 80%

(F7) HPMC K4M 75% & EC 5%

(F8) HPMC K4M 70% & EC 10%

(F9) HPMC K4M 65% & EC 10%

(F10) HPMC K4M 60% & EC 20%

(F11) HPMC K15M 80%

(F12) HPMC K15M 75% & EC 5%

(F13) HPMC K15M 70% & EC 10%

(F14) HPMC K15M 65% & EC 15%

(F15) HPMC K15M 60% & EC 20%

(F16) MC 75%

(F17) MC 70% & EC 5%

(F18) MC 65% & EC 10%

(F19) MC 60% & EC 15%

(F20) MC 55% & EC 20%

FIGURE 8: SWELLING INDEX OF ALL FORMULATIONS

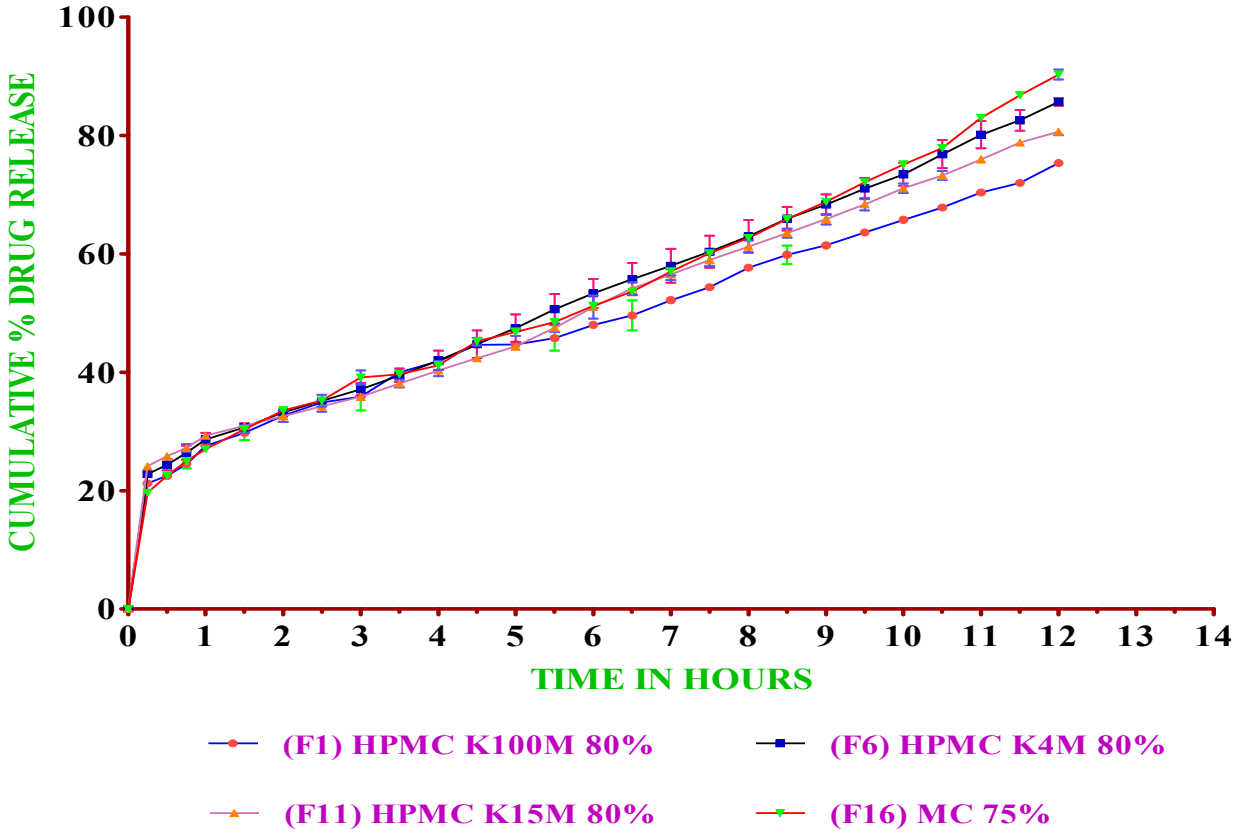


FIGURE 9: *IN VITRO* RELEASE PROFILE OF VALSARTAN FLOATING MATRIX TABLETS CONTAINING HYDROPHILIC POLYMERS

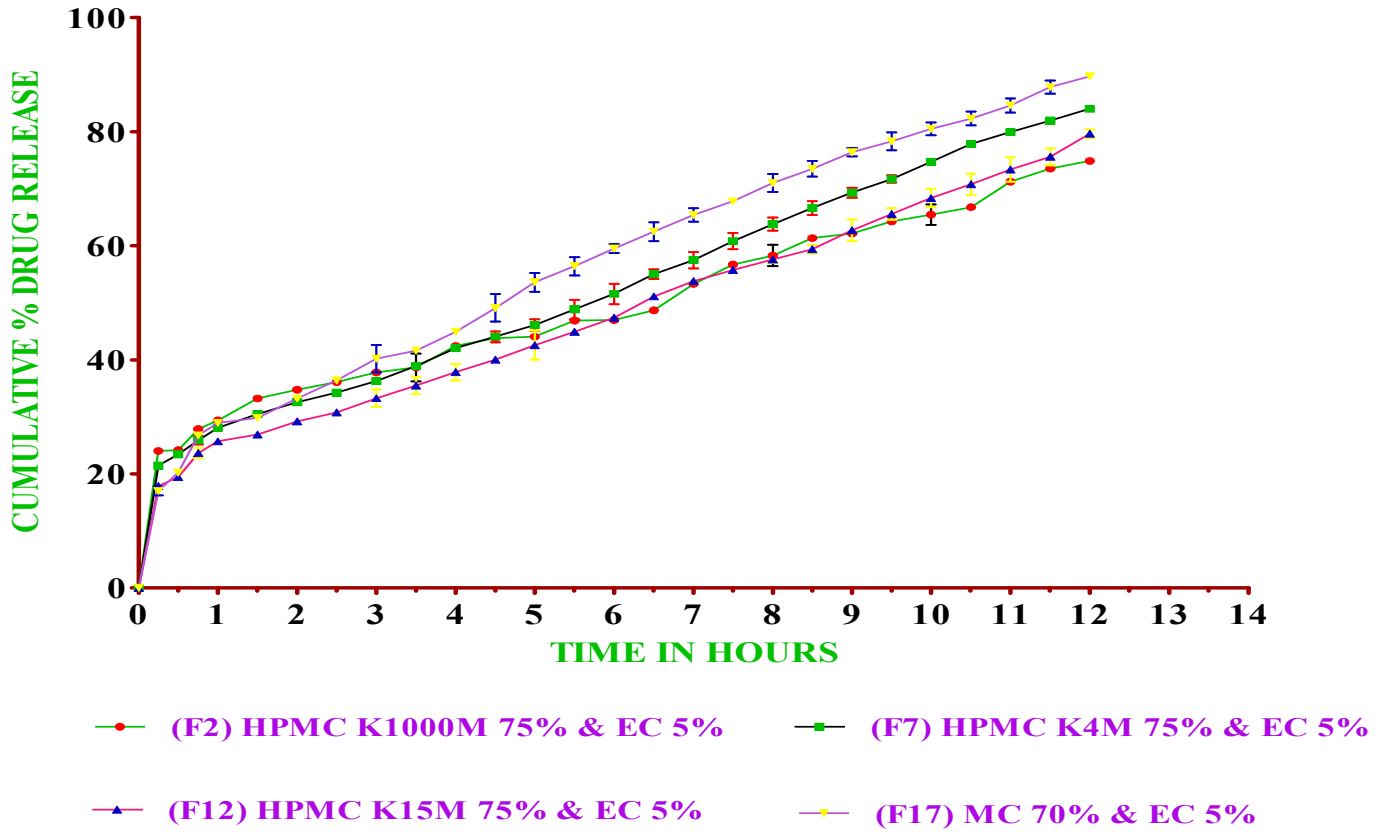


FIGURE 10: *IN VITRO* RELEASE PROFILE OF VALSARTAN FLOATING MATRIX TABLETS CONTAINING COMBINATION OF HYDROPHILIC AND HYDROPHOBIC POLYMERS

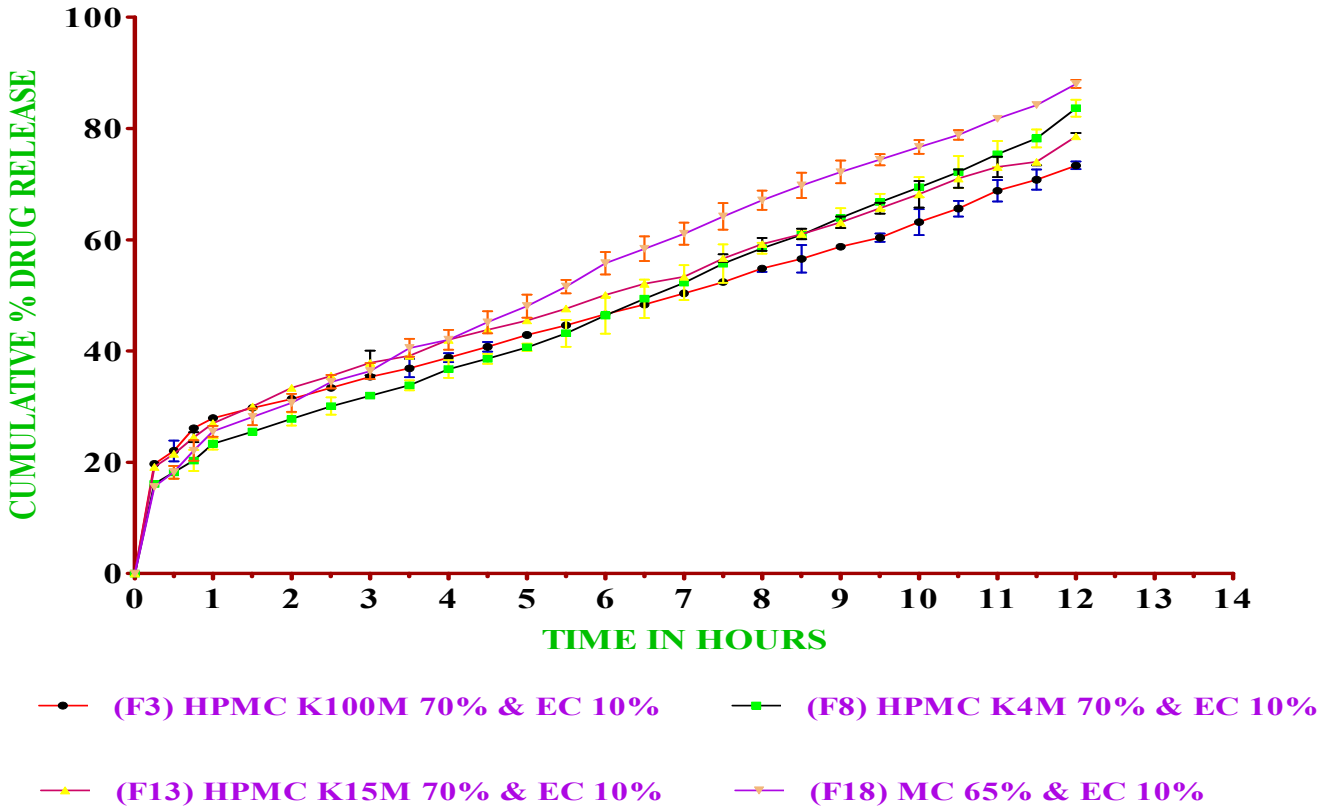


FIGURE 11: *IN VITRO* RELEASE PROFILE OF VALSARTAN FLOATING MATRIX TABLETS CONTAINING COMBINATION OF HYDROPHILIC AND HYDROPHOBIC POLYMERS

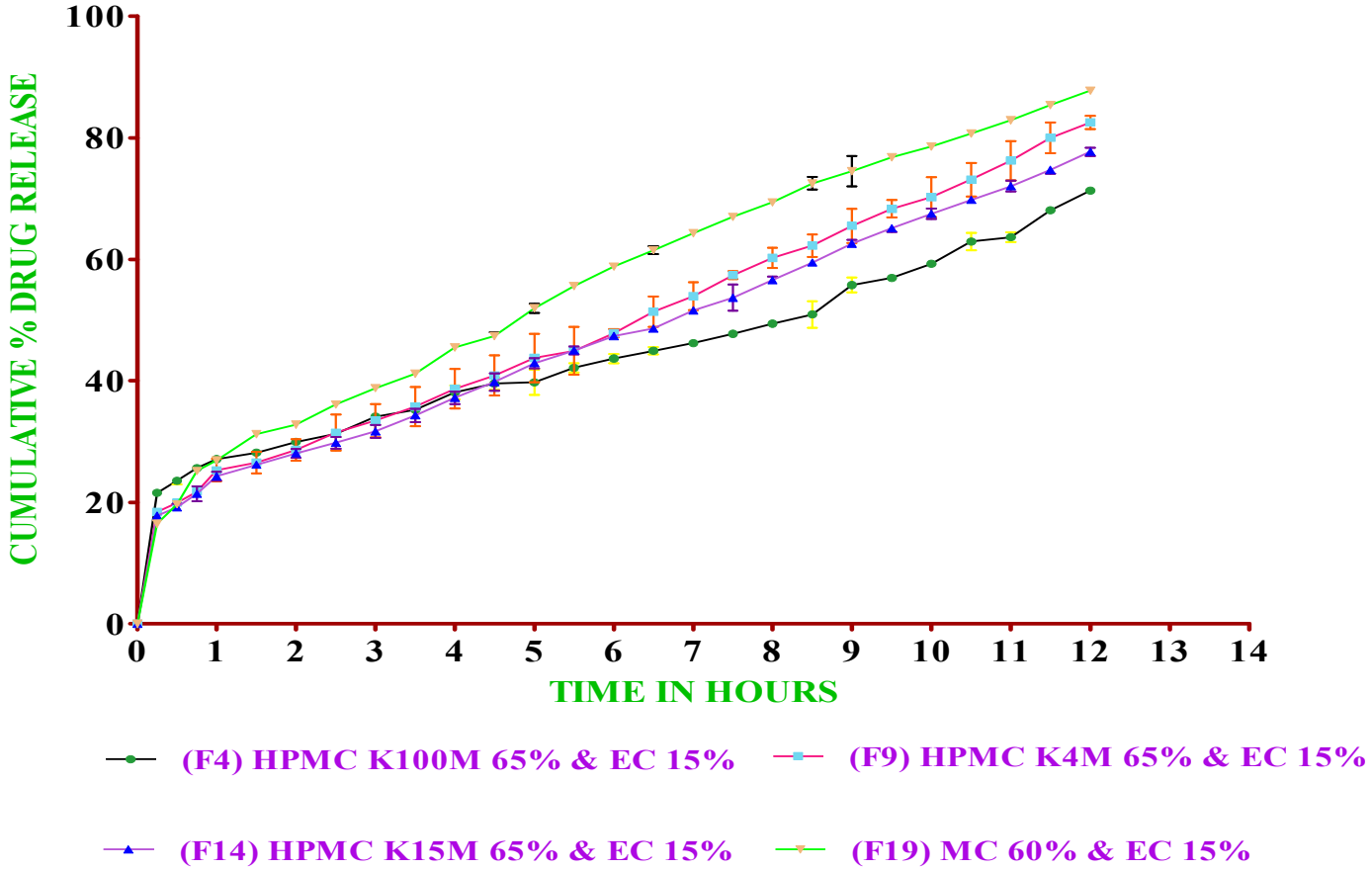


FIGURE 12: *IN VITRO* RELEASE PROFILE OF VALSARTAN FLOATING MATRIX TABLETS CONTAINING COMBINATION OF HYDROPHILIC AND HYDROPHOBIC POLYMERS

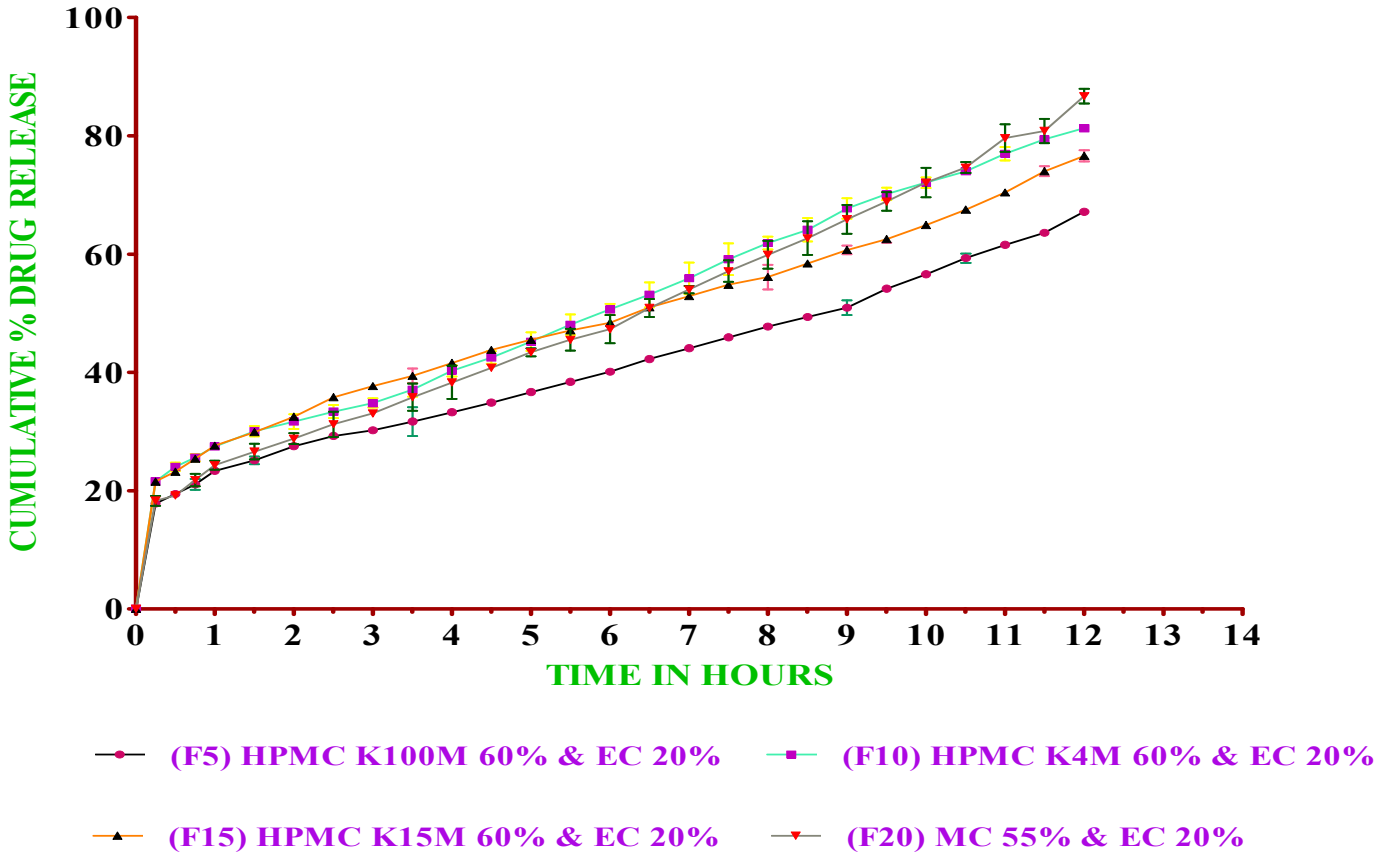
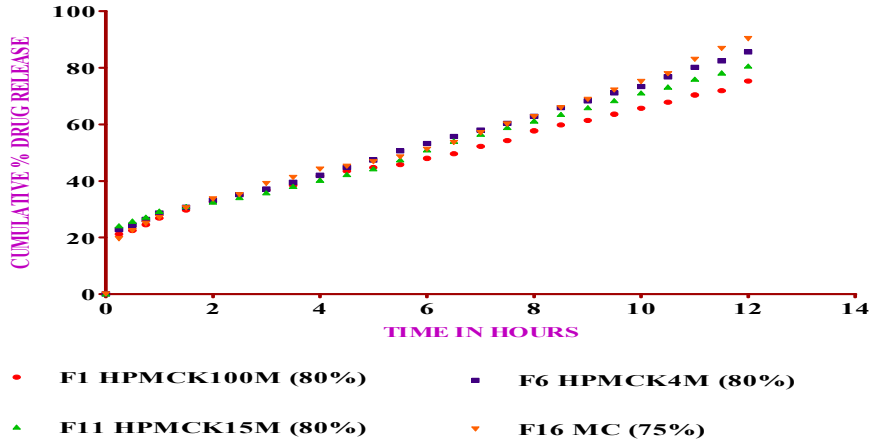
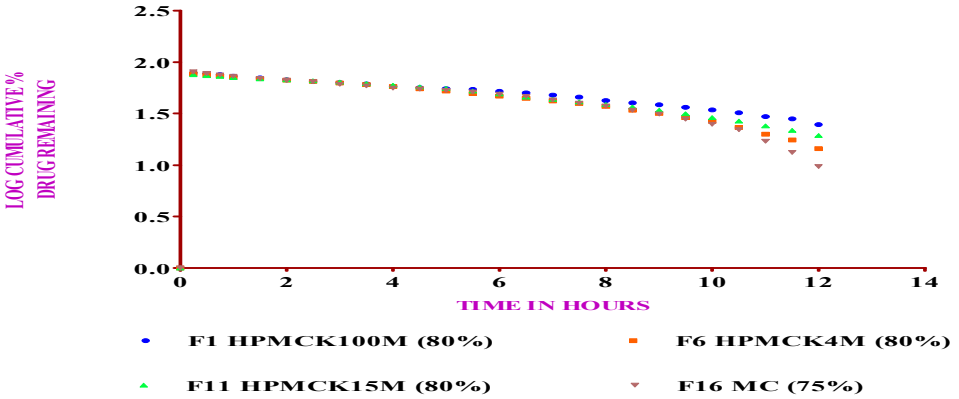


FIGURE 13: *IN VITRO* RELEASE PROFILE OF VALSARTAN FLOATING MATRIX TABLETS CONTAINING COMBINATION OF HYDROPHILIC AND HYDROPHOBIC POLYMERS

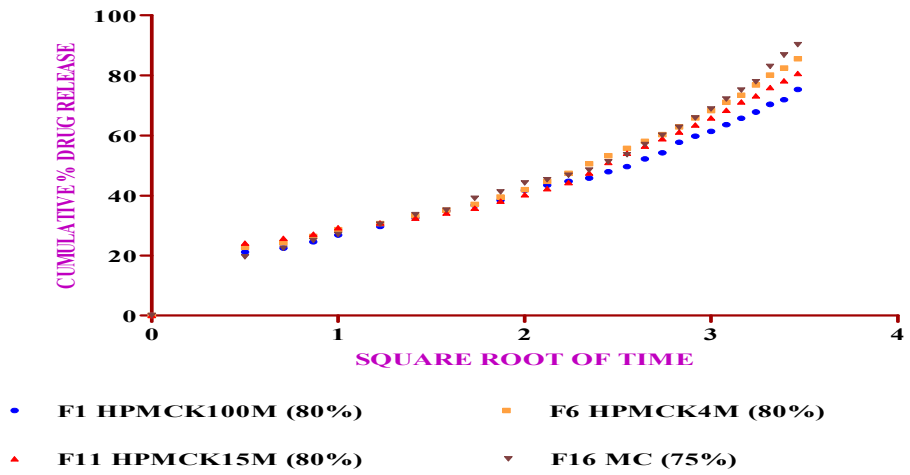
COMPARISON OF INVITRO ZERO ORDER RELEASE KINETICS OF HYDROPHILIC POLYMERS



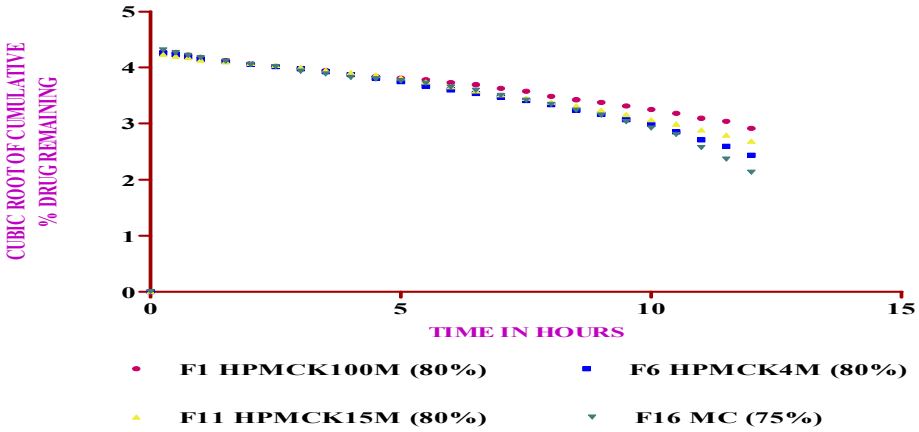
COMPARISON OF INVITRO FIRST ORDER RELEASE KINETICS OF HYDROPHILIC POLYMERS



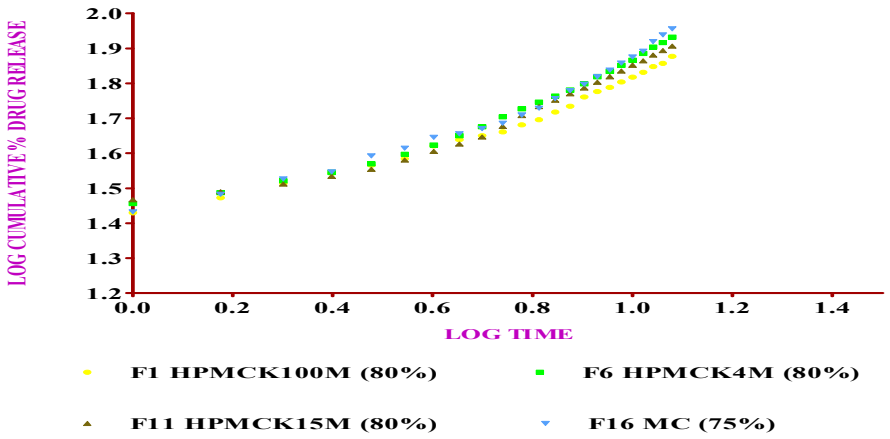
COMPARISON OF INVITRO HIGUCHI MODEL RELEASE KINETICS OF HYDROPHILIC POLYMERS



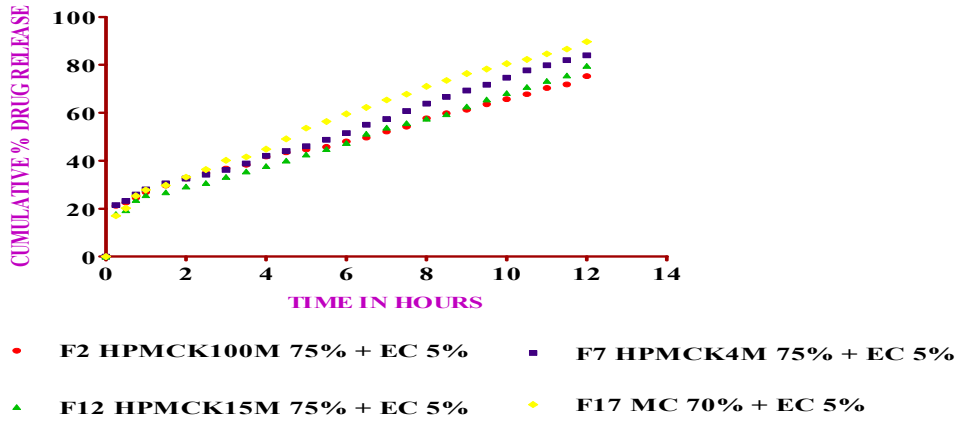
COMPARISON OF INVITRO HIXSON CROWELL MODEL RELEASE KINETICS OF HYDROPHILIC POLYMERS



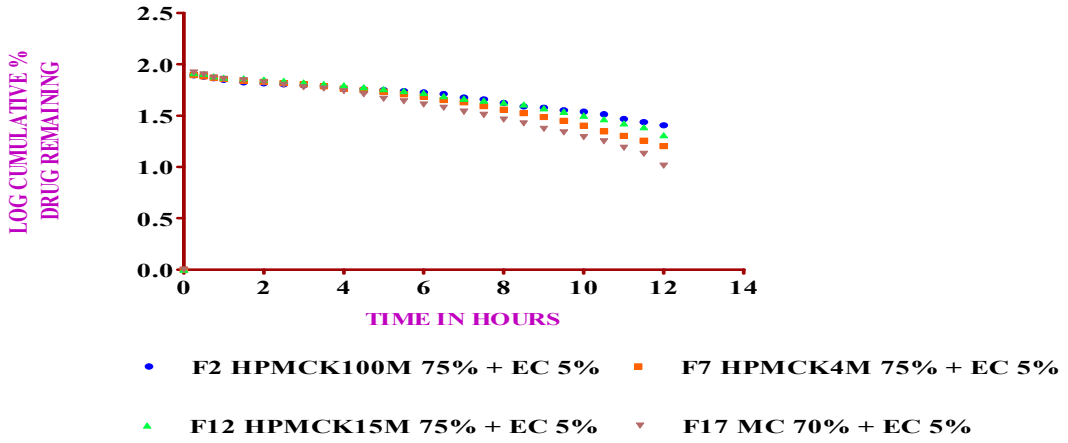
COMPARISON OF INVITRO KORSEMEYER PEPPAS MODEL RELEASE KINETICS OF HYDROPHILIC POLYMERS



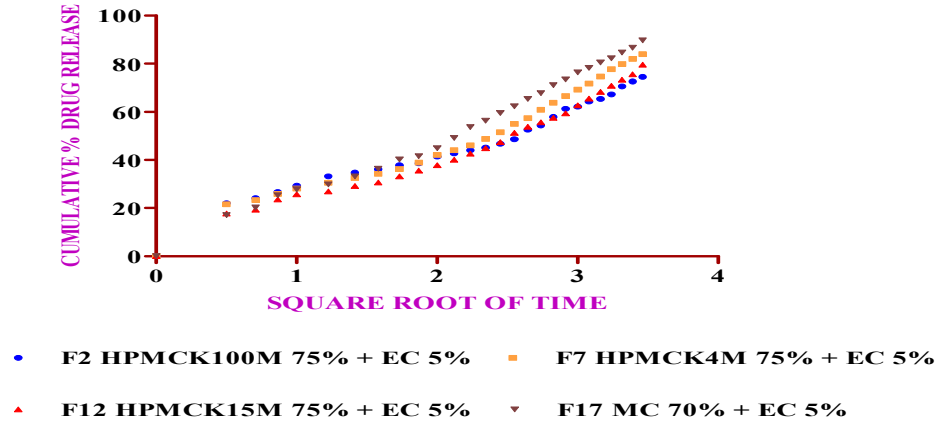
COMPARISON OF *INVITRO* ZERO ORDER RELEASE KINETICS OF HYDROPHILIC POLYMERS & HYDROPHOBIC POLYMERS



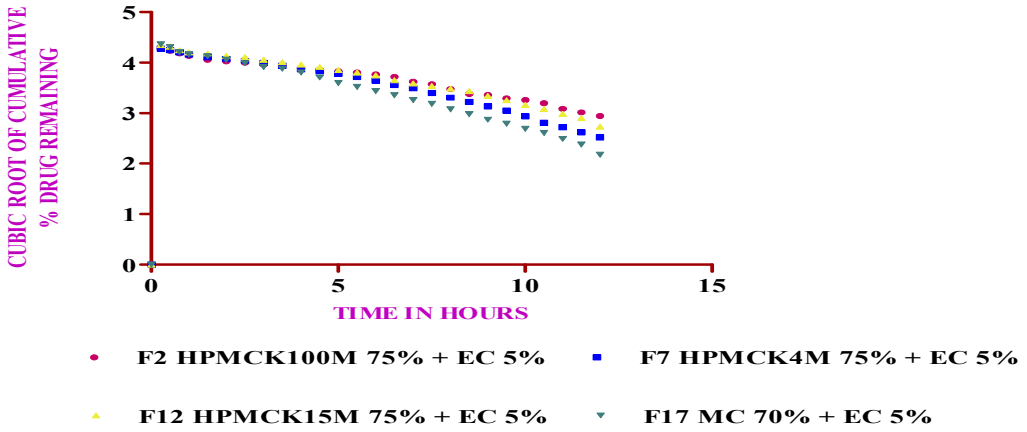
COMPARISON OF *INVITRO* FIRST ORDER RELEASE KINETICS OF HYDROPHILIC POLYMERS & HYDROPHOBIC POLYMERS



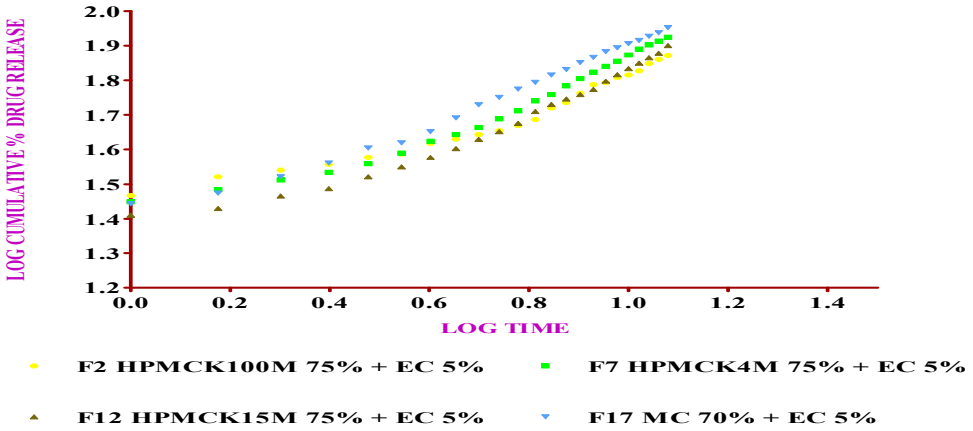
COMPARISON OF *INVITRO* HIGUCHI MODEL RELEASE KINETICS OF HYDROPHILIC POLYMERS & HYDROPHOBIC POLYMERS



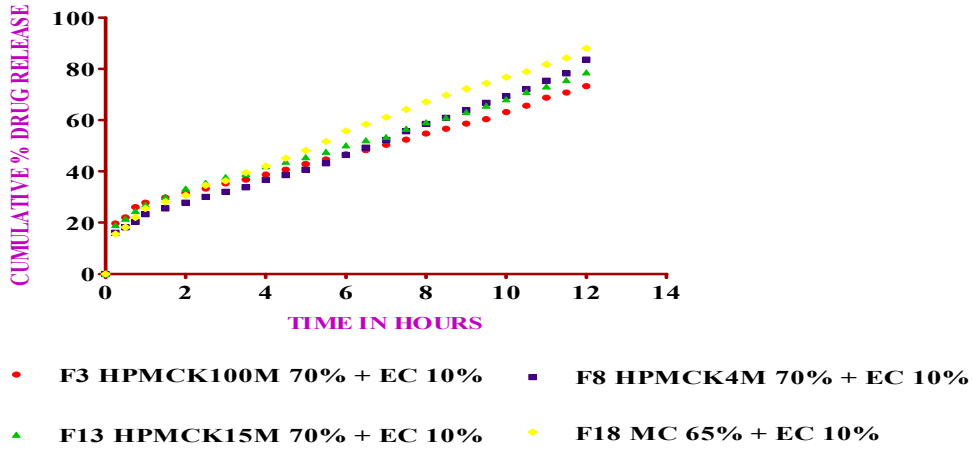
COMPARISON OF *INVITRO* HIXSON CROWELL MODEL RELEASE KINETICS OF HYDROPHILIC POLYMERS & HYDROPHOBIC POLYMERS



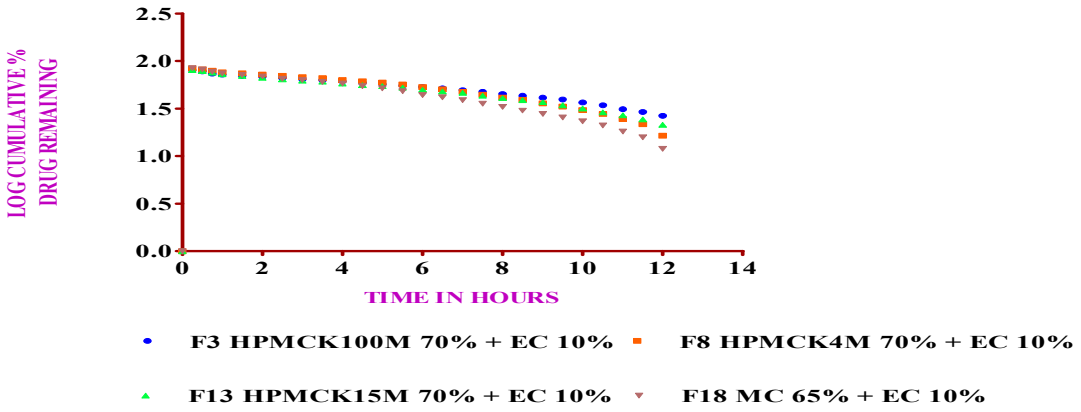
COMPARISON OF *INVITRO* KORSMEYER PEPPAS MODEL RELEASE KINETICS OF HYDROPHILIC POLYMERS & HYDROPHOBIC POLYMERS



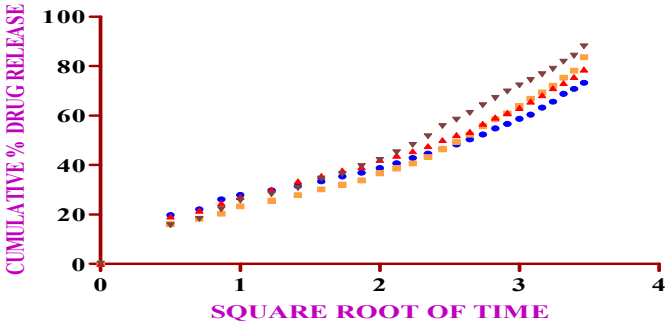
COMPARISON OF *INVITRO* ZERO ORDER RELEASE KINETICS OF HYDROPHILIC POLYMERS & HYDROPHOBIC POLYMERS



COMPARISON OF *INVITRO* FIRST ORDER RELEASE KINETICS OF HYDROPHILIC POLYMERS & HYDROPHOBIC POLYMERS



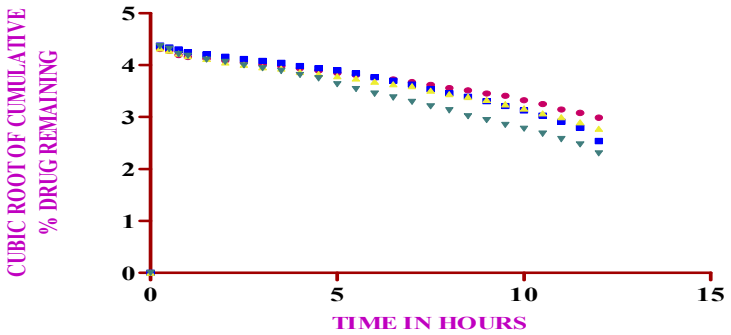
COMPARISON OF *INVITRO* HIGUCHI MODEL RELEASE KINETICS OF HYDROPHILIC POLYMERS & HYDROPHOBIC POLYMERS



F3 HPMCK100M 70% + EC 10% F8 HPMCK4M 70% + EC 10%

F13 HPMCK15M 70% + EC 10% F18 MC 65% + EC 10%

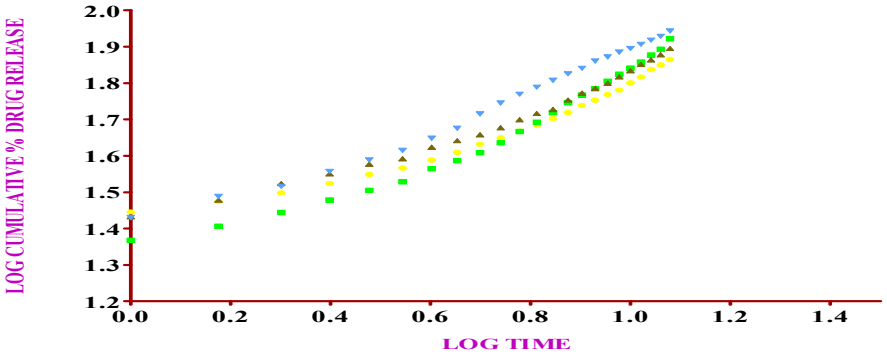
COMPARISON OF *INVITRO* HIXSON CROWELL RELEASE KINETICS OF HYDROPHILIC POLYMERS & HYDROPHOBIC POLYMERS



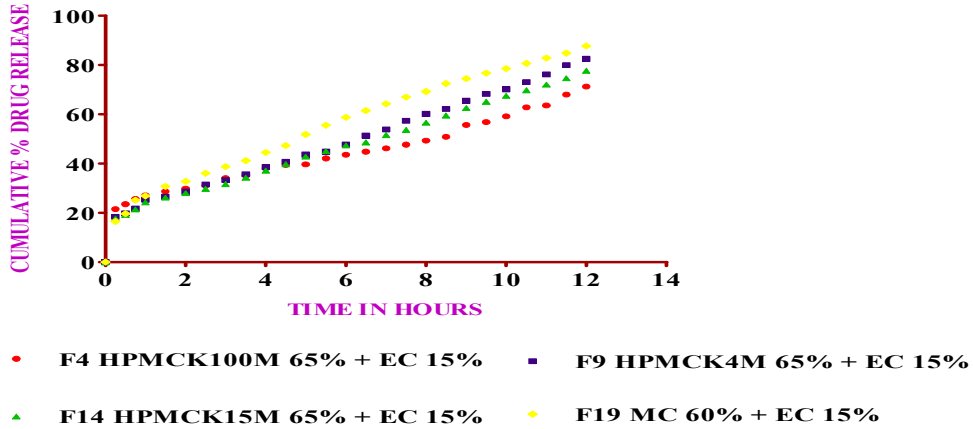
F3 HPMCK100M 70% + EC 10% F8 HPMCK4M 70% + EC 10%

F13 HPMCK15M 70% + EC 10% F18 MC 70% + EC 10%

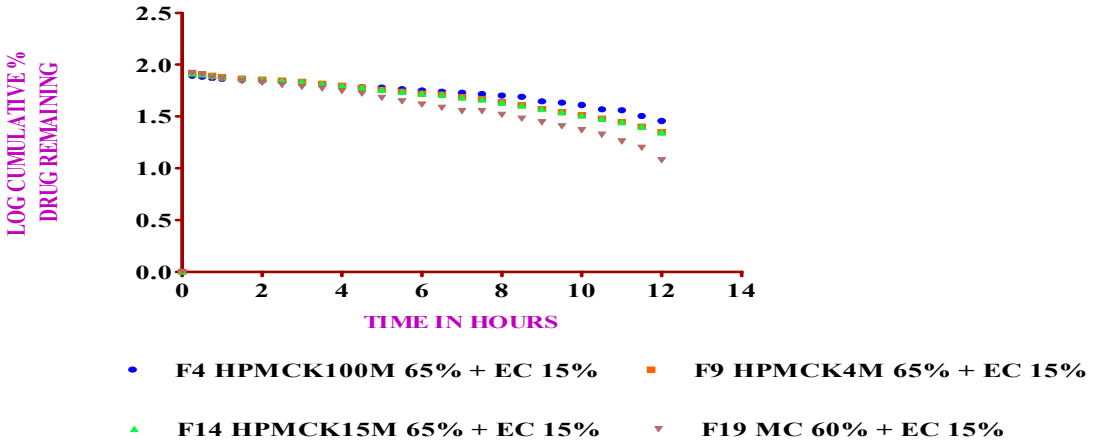
COMPARISON OF *INVITRO* KORSMEYER PEPPAS MODEL RELEASE KINETICS OF HYDROPHILIC POLYMERS & HYDROPHOBIC POLYMERS



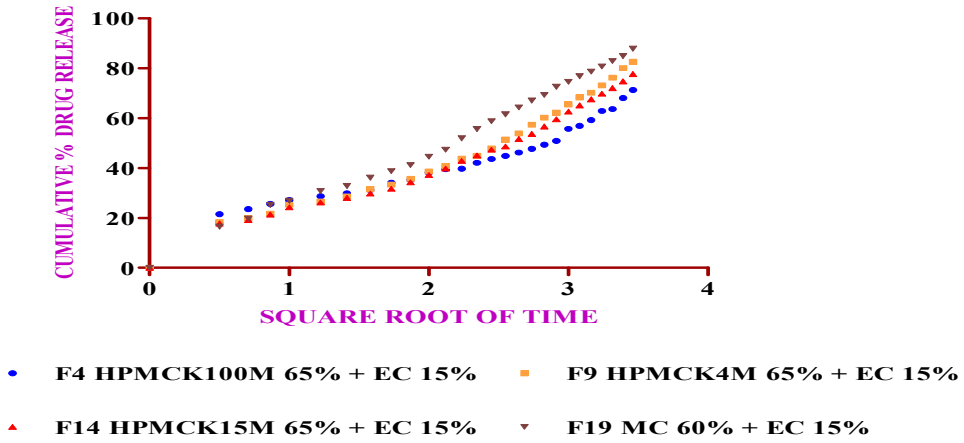
COMPARISON OF *INVITRO* ZERO ORDER RELEASE KINETICS OF HYDROPHILIC POLYMERS & HYDROPHOBIC POLYMERS



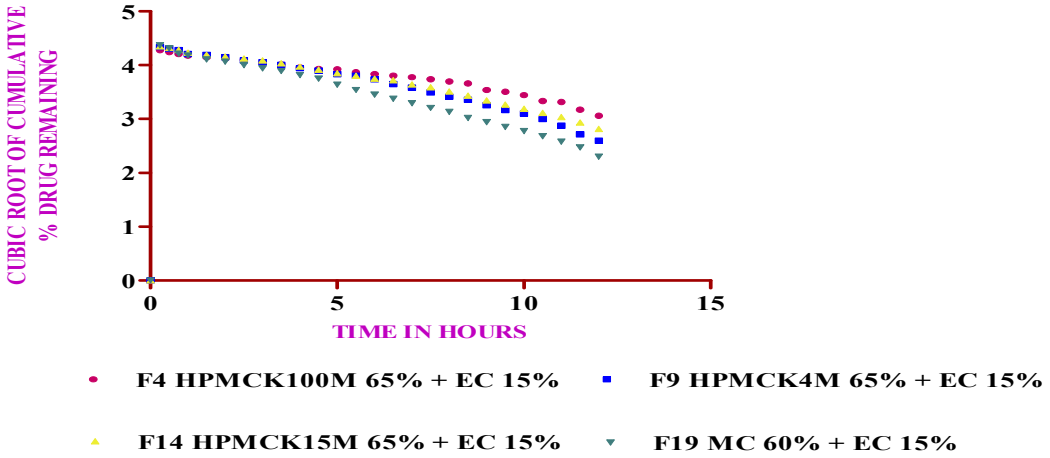
COMPARISON OF *INVITRO* FIRST ORDER RELEASE KINETICS OF HYDROPHILIC POLYMERS & HYDROPHOBIC POLYMERS



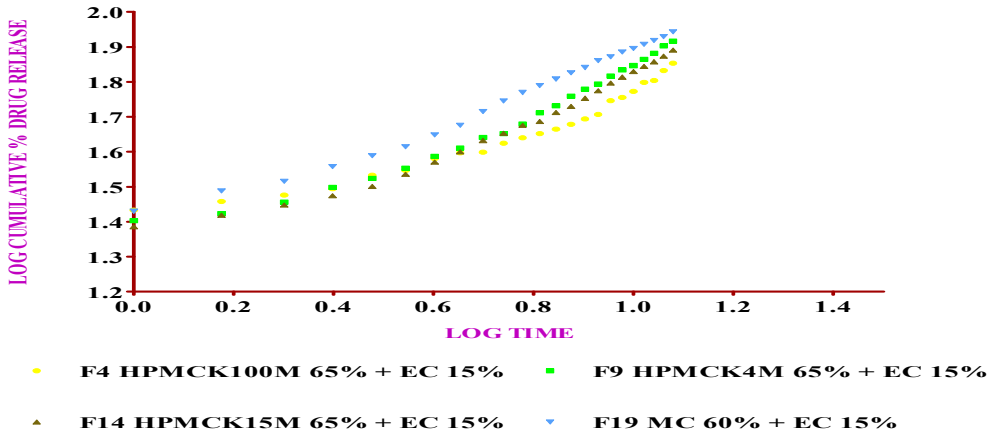
COMPARISON OF *INVITRO* HIGUCHI MODEL RELEASE KINETICS OF HYDROPHILIC POLYMERS & HYDROPHOBIC POLYMERS



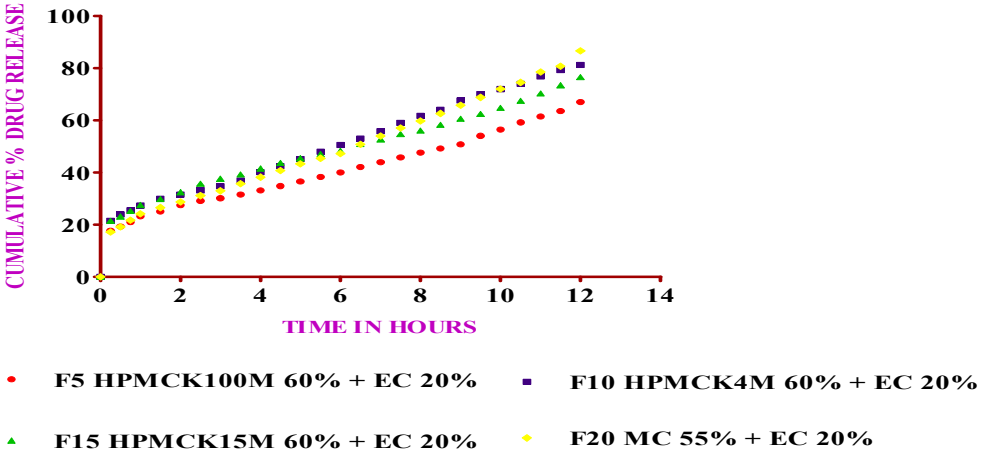
COMPARISON OF *INVITRO* HIXSON CROWELL MODEL RELEASE KINETICS OF HYDROPHILIC POLYMERS & HYDROPHOBIC POLYMERS



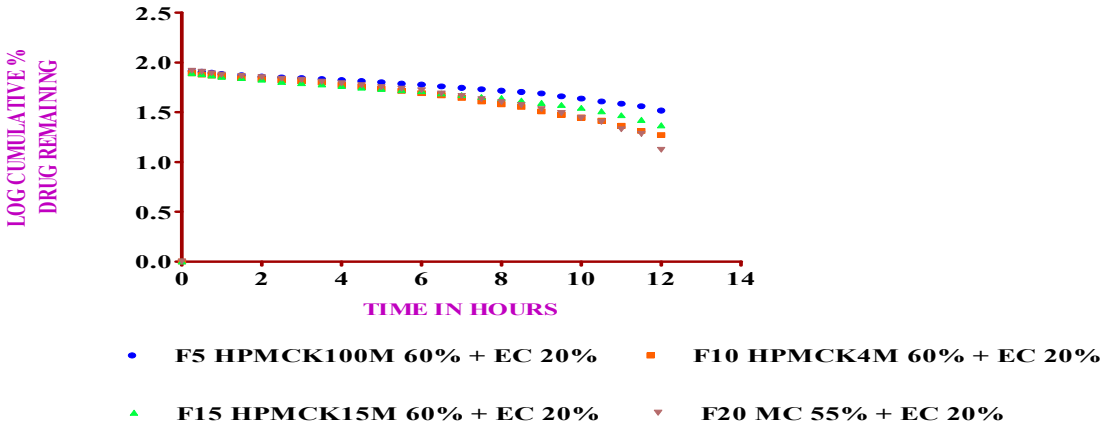
COMPARISON OF *INVITRO* KORSMEYER PEPPAS MODEL RELEASE KINETICS OF HYDROPHILIC POLYMERS & HYDROPHOBIC POLYMERS



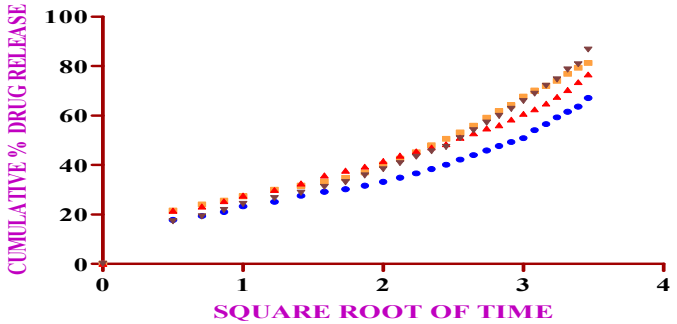
COMPARISON OF *INVITRO* ZERO ORDER RELEASE KINETICS OF HYDROPHILIC POLYMERS & HYDROPHOBIC POLYMERS



COMPARISON OF *INVITRO* FIRST ORDER RELEASE KINETICS OF HYDROPHILIC POLYMERS & HYDROPHOBIC POLYMERS



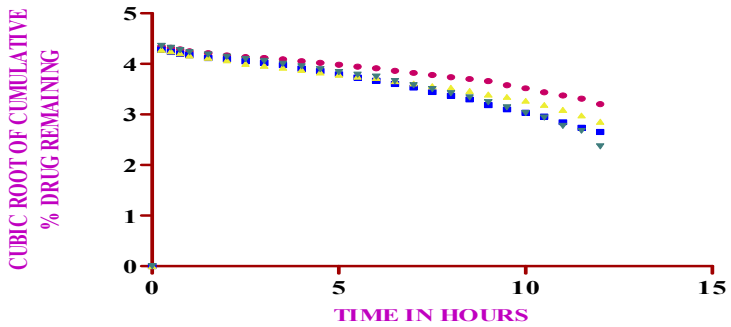
COMPARISON OF *INVITRO* HIGUCHI MODEL RELEASE KINETICS OF HYDROPHILIC POLYMERS & HYDROPHOBIC POLYMERS



F5 HPMCK100M 60% + EC 20% F10 HPMCK4M 60% + EC 20%

F15 HPMCK15M 60% + EC 20% F20 MC 55% + EC 20%

COMPARISON OF *INVITRO* HIXSON CROWELL MODEL RELEASE KINETICS OF HYDROPHILIC POLYMERS & HYDROPHOBIC POLYMERS



F5 HPMCK100M 60% + EC 20% F10 HPMCK4M 60% + EC 20%

F15 HPMCK15M 60% + EC 20% F20 MC 55% + EC 20%

COMPARISON OF *INVITRO* KORSMEYER PEPPAS MODEL RELEASE KINETICS OF HYDROPHILIC POLYMERS & HYDROPHOBIC POLYMERS

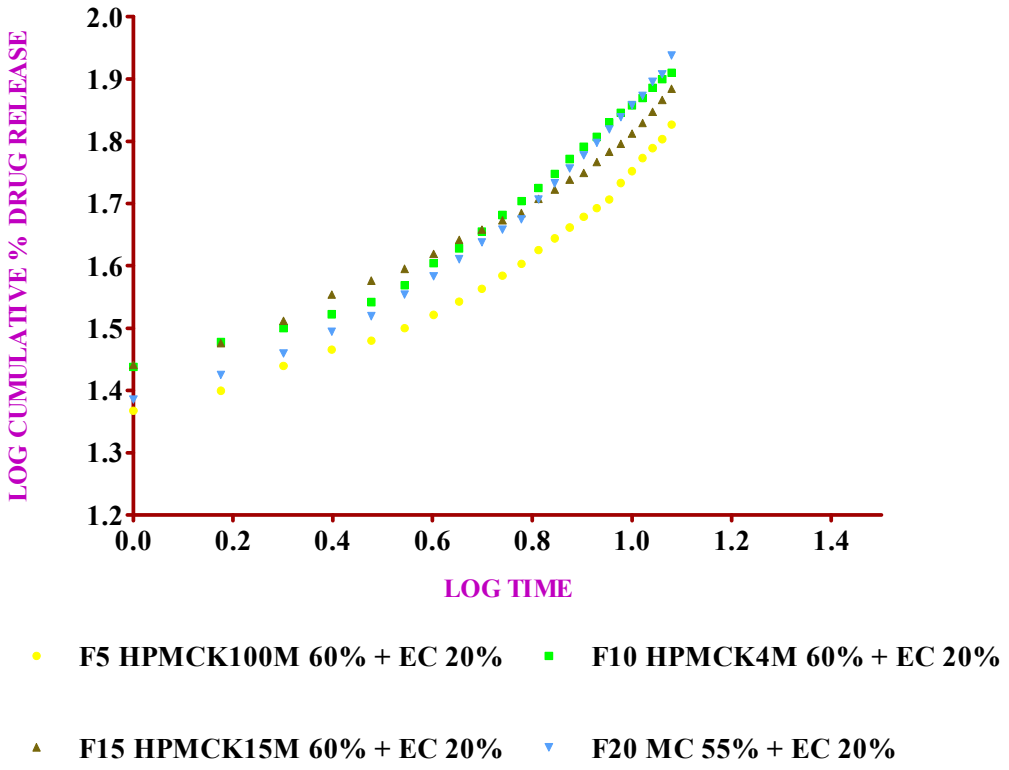


FIGURE 14: *INVITRO* DRUG RELEASE KINETICS

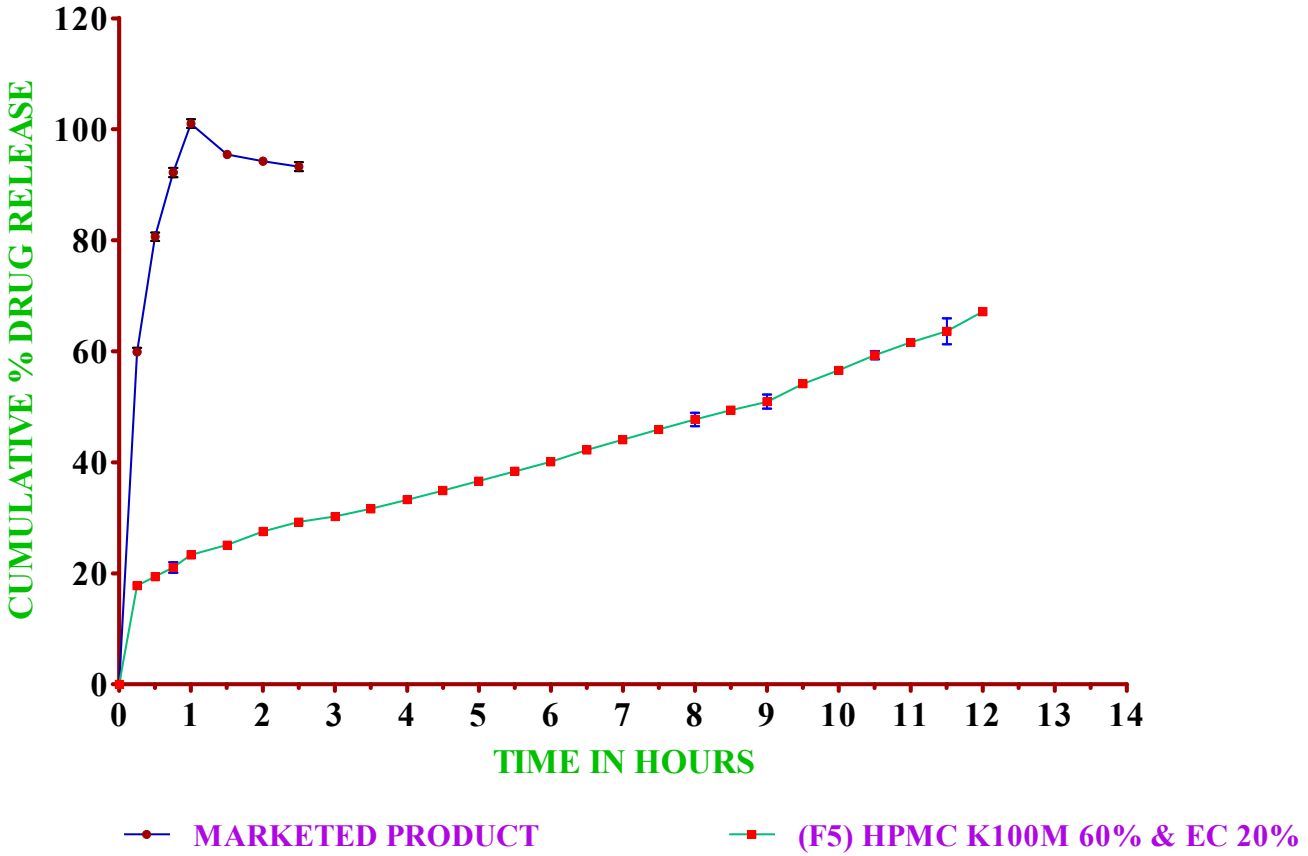
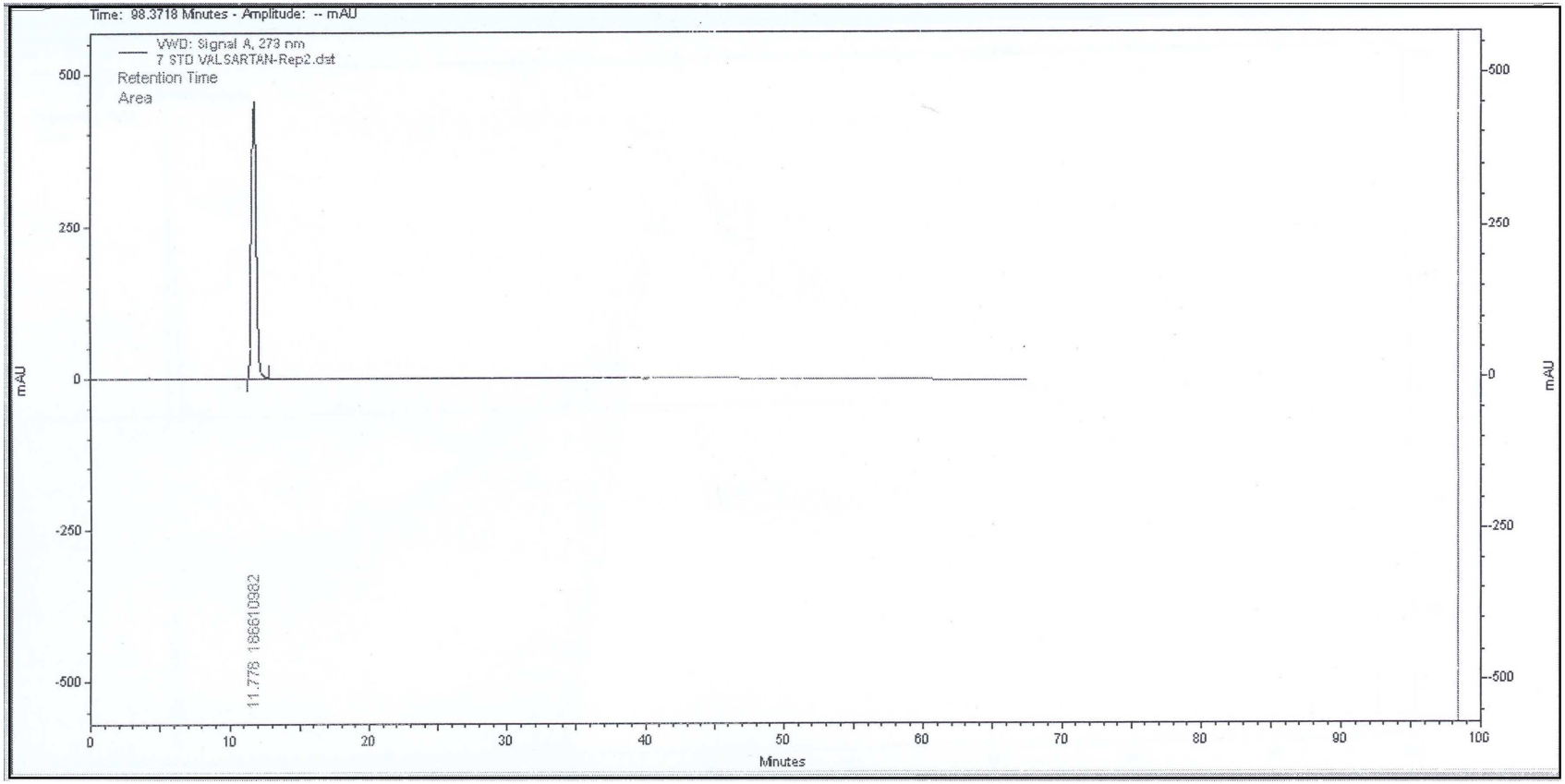
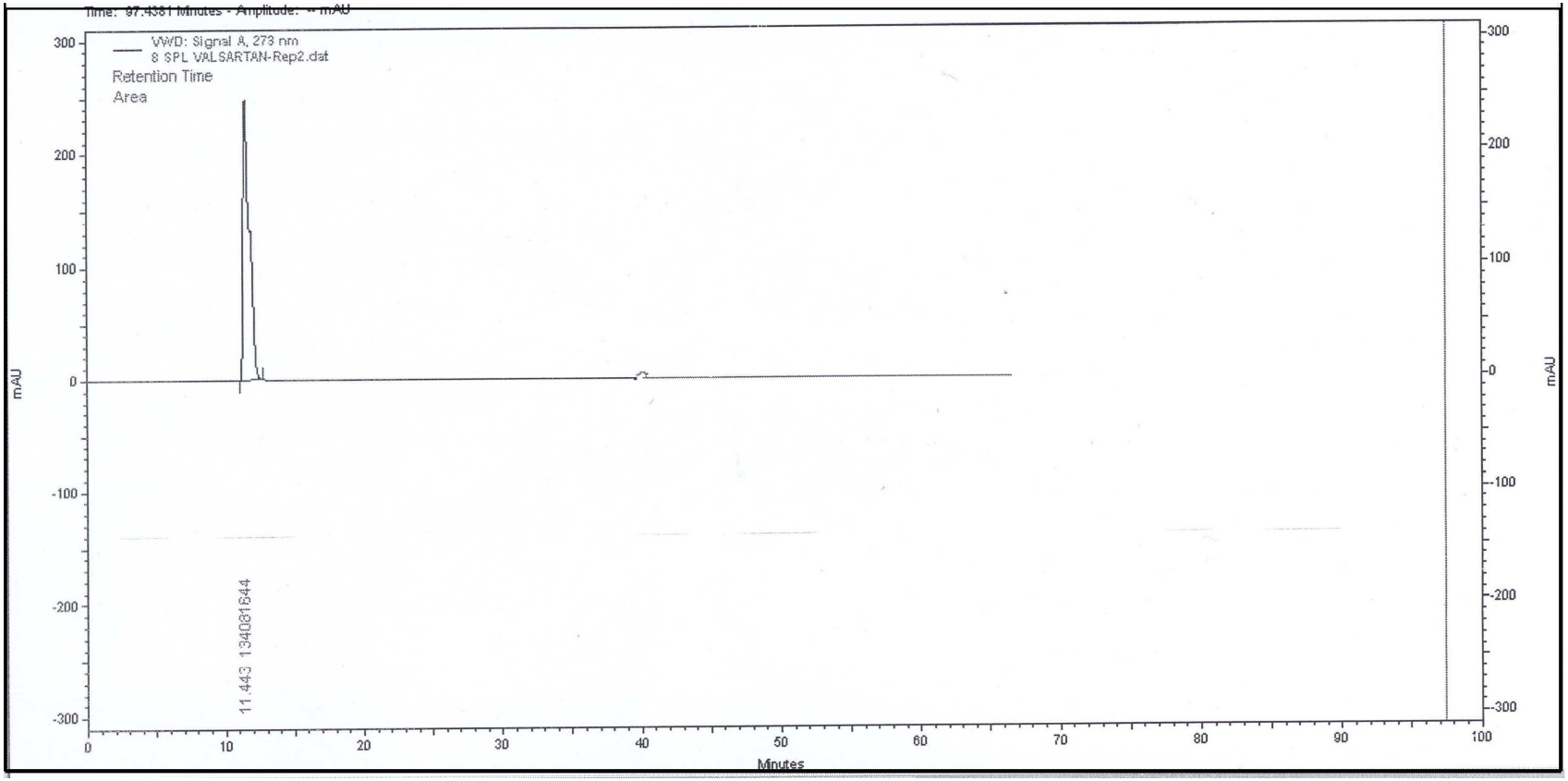


FIGURE 15: *IN VITRO* RELEASE PROFILE OF BEST FORMULATION COMPARED WITH MARKETED PRODUCT

HPLC CHROMATOGRAM OF VALSARTAN IN THE MOBILE PHASE



(A) RETENTION TIME AREA OF STANDARD VALSARTAN



(B) RETENTION TIME AREA OF SAMPLE VALSARTAN (BEST FORMULATION)

FIGURE 16: (A) ***RETENTION TIME AREA OF STANDARD VALSARTAN,***
(B) RETENTION TIME AREA OF SAMPLE VALSARTAN (BEST FORMULATION)

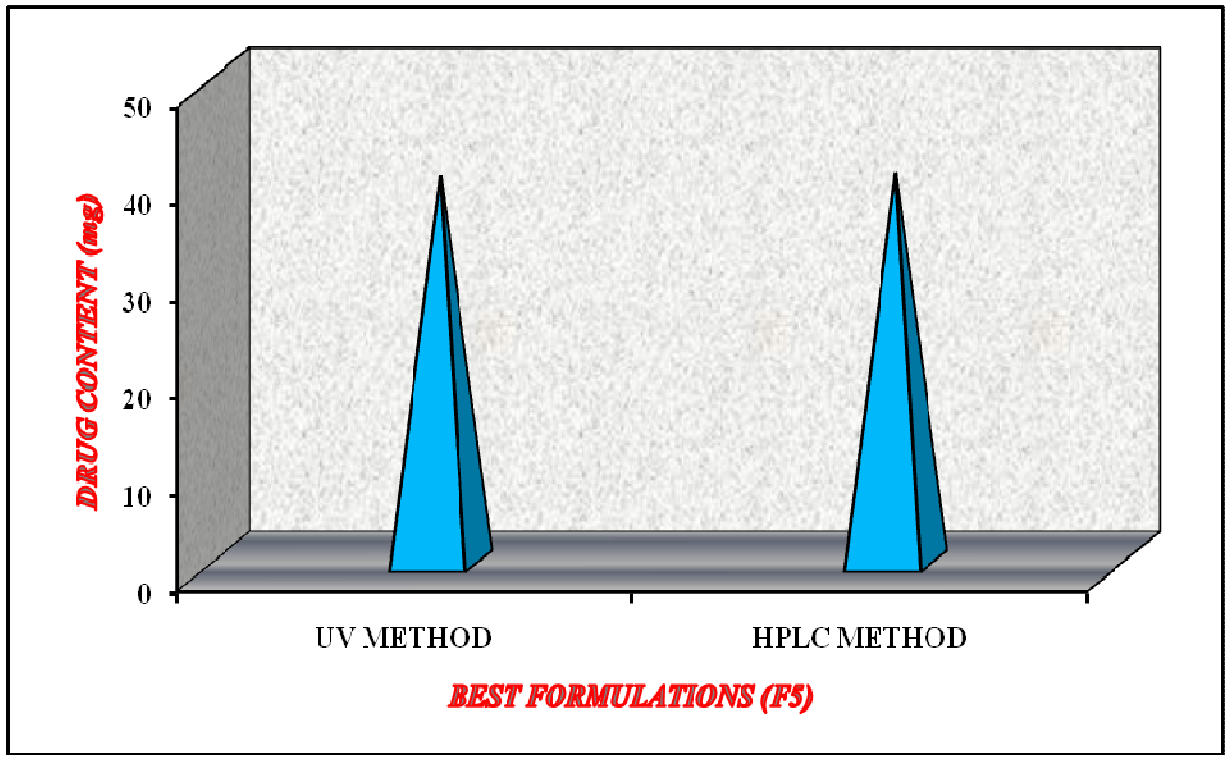
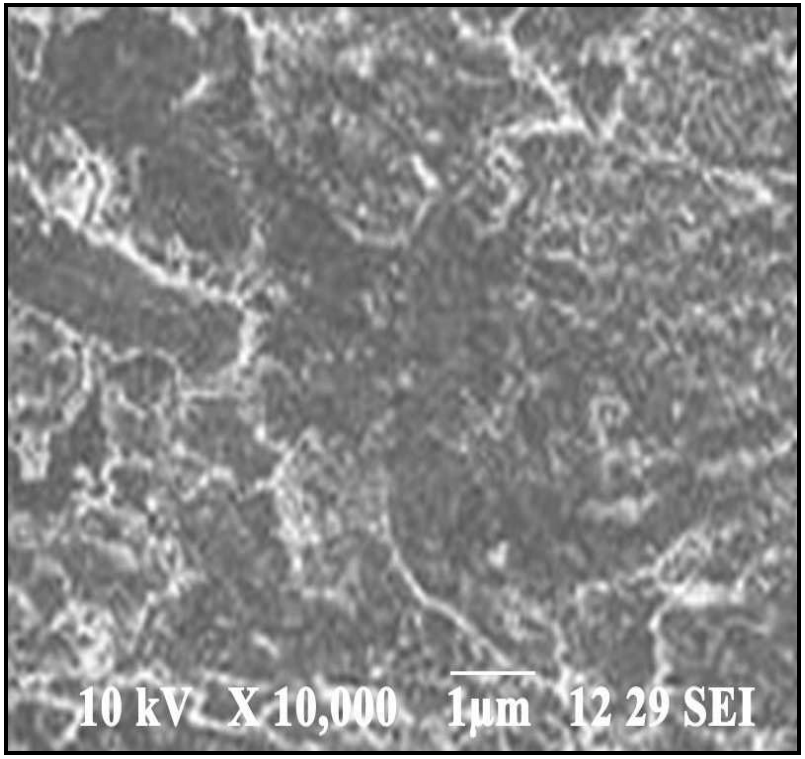
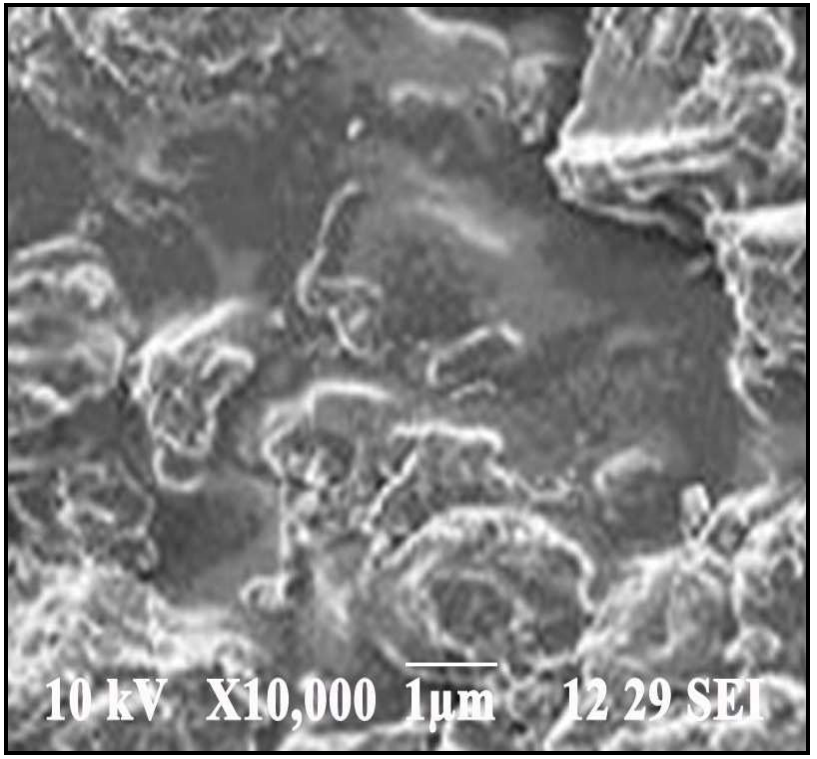


FIGURE 17: COMPARISON OF DRUG CONTENT OF VALSARTAN FLOATING MATRIX TABLET (BEST FORMULATION) BY UV AND HPLC METHOD



BEFORE



AFTER

FIGURE 18: SCANNING ELECTRON MICROSCOPY IMAGES OF TABLET SURFACES (BEST FORMULATION) BEFORE AND AFTER DISSOLUTION

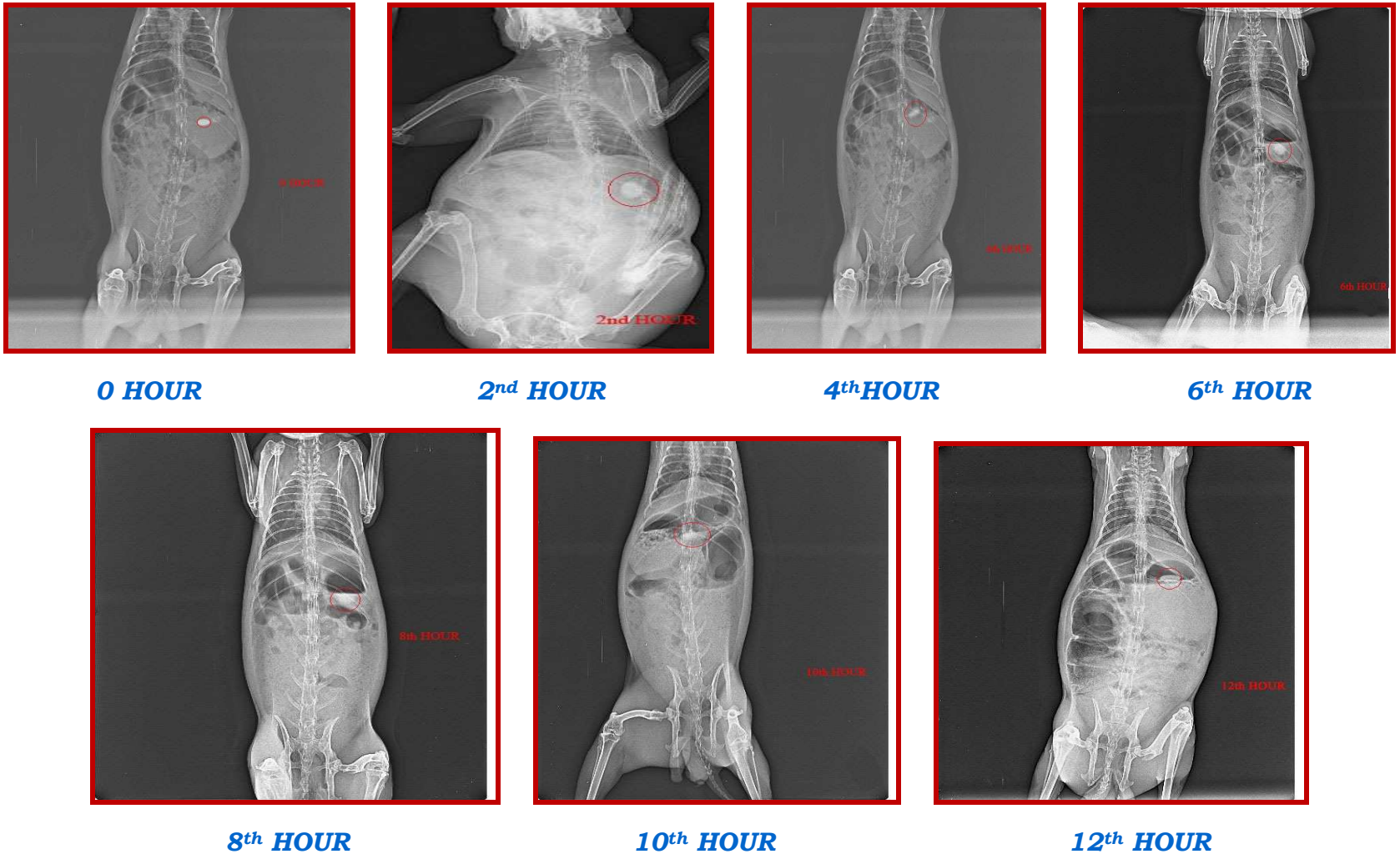


FIGURE 19 : *IN VIVO* X-RAY PHOTOGRAPHS OF VALSARTAN FLOATING MATRIX TABLET (BEST FORMULATION)

TABLE: 1- CALIBRATION OF VALSARTAN IN 0.1N HYDROCHLORIC ACID

S.No.	*CONCENTRATION (µg/ml)*	*ABSORBANCE ± SD**
1.	2	0.188 ± 0.006
2.	4	0.386 ± 0.008
3.	6	0.593 ± 0.004
4.	8	0.771 ± 0.014
5.	10	0.953 ± 0.013
6.	12	1.124 ± 0.011
7.	14	1.319 ± 0.016
8.	16	1.495 ± 0.022
9.	18	1.704 ± 0.017
10.	20	1.893 ± 0.018

n = 3* **γ = 0.99980**

TABLE: 2A- COMPOSITION OF VALSARTAN FLOATING MATRIX TABLETS (F1 – F10)

S.NO	*INGREDIENTS*	*QUANTITY FOR 1 TABLET (mg)*									
		F1	***F2***	***F3***	***F4***	***F5***	***F6***	***F7***	***F8***	***F9***	***F10***
1.	Valsartan	40	40	40	40	40	40	40	40	40	40
2.	HPMC K100M	200	187.5	175	162.5	150	-	-	-	-	-
3.	HPMC K4M	-	-	-	-	-	200	187.5	175	162.5	150
4.	HPMC K15M	-	-	-	-	-	-	-	-	-	-
5.	Methylcellulose	-	-	-	-	-	-	-	-	-	-
6.	Ethyl cellulose	-	12.5	25	37.5	50	-	12.5	25	37.5	50
7.	Lactose	5	5	5	5	5	5	5	5	5	5
8.	Talc (1%)	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
9.	Magnesium Stearate (1%)	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Total Weight		**250**	**250**	**250**	**250**	**250**	**250**	**250**	**250**	**250**	**250**

TABLE: 2B- COMPOSITION OF VALSARTAN FLOATING MATRIX TABLETS (F11 – F20)

S.NO	*INGREDIENTS*	*QUANTITY FOR 1 TABLET (mg)*									
		F11	***F12***	***F13***	***F14***	***F15***	***F16***	***F17***	***F18***	***F19***	***F20***
1.	Valsartan	40	40	40	40	40	40	40	40	40	40
2.	HPMC K100M	-	-	-	-	-	-	-	-	-	-
3.	HPMC K4M	-	-	-	-	-	-	-	-	-	-
4.	HPMC K15M	200	187.5	175	162.5	150	-	-	-	-	-
5.	Methylcellulose	-	-	-	-	-	187.5	175	162.5	150	137.5
6.	Ethyl cellulose	-	12.5	25	37.5	50	-	12.5	25	37.5	50
7.	Lactose	5	5	5	5	5	17.5	17.5	17.5	17.5	17.5
8.	Talc (1%)	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
9.	Magnesium Stearate (1%)	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Total Weight		**250**	**250**	**250**	**250**	**250**	**250**	**250**	**250**	**250**	**250**

TABLE: 3A- PRECOMPRESSIONAL EVALUATION OF POWDER BLEND (F1 – F10)

FORMULATION CODE	*ANGLE OF REPOSE (θ) **	*BULK DENSITY (g/ml) **	*TAPPED DENSITY (g/ml) **	*COMPRESSIBILITY INDEX (%)**	*HAUSNER'S RATIO**	*% DRUG CONTENT **
F1	30º.13'	0.312	0.367	14.98	1.17	99.68
F2	29º.19'	0.297	0.390	23.8	1.21	99.79
F3	28º.17'	0.265	0.320	17.03	1.20	99.47
F4	29º.93'	0.290	0.390	25.0	1.24	99.37
F5	28º.09'	0.297	0.378	21.42	1.25	99.58
F6	28º.60'	0.277	0.367	24.46	1.22	99.58
F7	28º.53'	0.250	0.290	14	1.16	99.68
F8	28º.15'	0.265	0.357	24.9	1.24	99.26
F9	28º.03'	0.255	0.337	24.48	1.22	99.16
F10	27º.99'	0.347	0.446	22.19	1.18	99.16

n=3*

TABLE: 3B- PRECOMPRESSIONAL EVALUATION OF POWDER BLEND (F11 – F20)

FORMULATION CODE	*ANGLE OF REPOSE (θ) **	*BULK DENSITY (g/ml) **	*TAPPED DENSITY (g/ml) **	*COMPRESSIBILITY INDEX (%)**	*HAUSNER'S RATIO**	*% DRUG CONTENT **
F11	27º.08'	0.357	0.480	25.03	1.24	99.26
F12	29º.53'	0.367	0.480	23.5	1.20	99.26
F13	28º.24'	0.357	0.462	22.7	1.24	99.16
F14	29º.54'	0.312	0.416	24.98	1.20	99.16
F15	30º.26'	0.320	0.416	23.06	1.19	99.05
F16	28º.50'	0.297	0.357	16	1.19	98.95
F17	28º.34'	0.296	0.416	20.6	1.20	98.84
F18	28º.35'	0.284	0.357	20.4	1.25	98.63
F19	28º.17'	0.337	0.415	18.9	1.23	98.68
F20	28º.24'	0.271	0.357	23.91	1.21	98.32

n=3*

TABLE: 4A- POSTCOMPRESSIONAL EVALUATION OF VALSARTAN FLOATING MATRIX TABLETS (F1 – F10)

FORMULATION CODE	*GENERAL APPEARANCE*	*HARDNESS (kg/cm^2)**	*THICKNESS (mm)**	*DIAMETER (mm)**	*FRIABILITY (%)**	*WEIGHT VARIATION (mg)**	*% DRUG CONTENT **
F1	White color, biconvex shaped	3	4	10	0.13	249.54	99.79
F2	White color, biconvex shaped	4	4	10	0.25	249.17	99.58
F3	White color, biconvex shaped	4	4	10	0.27	248.09	99.37
F4	White color, biconvex shaped	4	4	10	0.22	247.00	99.47
F5	White color, biconvex shaped	4	4	10	0.28	249.03	99.79
F6	White color, biconvex shaped	4	3.9	10	0.23	246.91	99.47
F7	White color, biconvex shaped	4	3.9	10	0.38	247.64	99.47
F8	White color, biconvex shaped	4	3.9	10	0.21	247.80	99.37
F9	White color, biconvex shaped	4	3.9	10	0.36	246.71	99.79
F10	White color, biconvex shaped	4	3.9	10	0.30	244.25	99.58

n=3*

TABLE: 4B- POSTCOMPRESSIONAL EVALUATION OF VALSARTAN FLOATING MATRIX TABLETS (F11 – F20)

FORMULATION CODE	*GENERAL APPEARANCE*	*HARDNESS (kg/cm^2)**	*THICKNESS (mm)**	*DIAMETER (mm)**	*FRIABILITY (%)**	*WEIGHT VARIATION (mg)**	*% DRUG CONTENT **
F11	White color, biconvex shaped	4	3.9	10	0.27	247.99	99.79
F12	White color, biconvex shaped	4	3.9	10	0.35	247.76	99.89
F13	White color, biconvex shaped	3.5	3.9	10	0.43	246.50	99.58
F14	White color, biconvex shaped	4	3.9	10	0.28	246.58	99.37
F15	White color, biconvex shaped	4	3.9	10	0.23	247.54	99.37
F16	White color, biconvex shaped	3	3.5	10	0.32	245.64	99.27
F17	White color, biconvex shaped	3.5	3.5	10	0.29	247.73	99.35
F18	White color, biconvex shaped	3.5	3.9	10	0.50	248.18	99.79
F19	White color, biconvex shaped	4	3.9	10	0.25	248.74	99.16
F20	White color, biconvex shaped	3.5	3.9	10	0.30	248.08	98.63

n=3*

TABLE: 5A- *IN VITRO* BUOYANCY LAG TIME AND TOTAL FLOATING TIME OF VALSARTAN FLOATING MATRIX TABLETS (F1 – F10)

FORMULATION CODE	***BUOYANCY LAG TIME ****	***TOTAL FLOATING TIME (hrs) ****
F1	FLOATS IMMEDIATELY	>24hrs
F2	FLOATS IMMEDIATELY	>24hrs
F3	FLOATS IMMEDIATELY	>24hrs
F4	FLOATS IMMEDIATELY	>24hrs
F5	FLOATS IMMEDIATELY	>24hrs
F6	FLOATS IMMEDIATELY	>24hrs
F7	FLOATS IMMEDIATELY	>24hrs
F8	FLOATS IMMEDIATELY	>24hrs
F9	FLOATS IMMEDIATELY	>24hrs
F10	FLOATS IMMEDIATELY	>24hrs

n=3*

TABLE: 5B- *IN VITRO* BUOYANCY LAG TIME AND TOTAL FLOATING TIME OF VALSARTAN FLOATING MATRIX TABLETS (F11 – F20)

FORMULATION CODE	***BUOYANCY LAG TIME ****	***TOTAL FLOATING TIME (hrs) ****
F11	FLOATS IMMEDIATELY	>24hrs
F12	FLOATS IMMEDIATELY	>24hrs
F13	FLOATS IMMEDIATELY	>24hrs
F14	FLOATS IMMEDIATELY	>24hrs
F15	FLOATS IMMEDIATELY	>24hrs
F16	10 Minutes	>24hrs
F17	3 Minutes 20 Seconds	>24hrs
F18	10 Minutes 15 Seconds	>24hrs
F19	15 Minutes	>24hrs
F20	8 Minutes 10 Seconds	>24hrs

n=3*

TABLE: 6A- *IN VITRO* SWELLING INDEX OF VALSARTAN FLOATING MATRIX TABLETS (F1 – F10)

FORMULATION CODE	***% SWELLING INDEX***					
	TIME IN HOURS					
	2	***4***	***6***	***8***	***10***	***12***
F1	63.9	72.3	77.1	79.2	81.5	81.5
F2	63.7	71.9	75.8	78.6	79.9	80.2
F3	59.3	68.7	74	77	79.4	80.2
F4	59.9	69.6	74.3	76.7	79.6	76.0
F5	58.2	67.9	73.1	73.9	76.8	75.7
F6	59.2	67.9	71.3	73.8	75.1	74.0
F7	54.8	61.9	67.2	68.8	70.7	68.7
F8	53.3	62.1	67.7	66.9	69.6	67.7
F9	54.7	63.3	67.2	67.3	67.2	65.7
F10	59.6	65.6	71.4	72.2	74.1	64.5

TABLE: 6B- *IN VITRO* SWELLING INDEX OF VALSARTAN FLOATING MATRIX TABLETS (F11 – F20)

FORMULATION CODE	***% SWELLING INDEX***					
	TIME IN HOURS					
	2	***4***	***6***	***8***	***10***	***12***
F11	64.8	69.8	73.1	74.7	75.3	75.0
F12	61.9	66.1	71.9	74.4	75	74.4
F13	59.4	69.9	70.3	72.6	73.3	74.6
F14	56.2	67.1	70.0	70.7	73.6	73.4
F15	53.1	63.4	67.9	70.2	68.3	66.1
F16	57.3	64.4	69.5	71.9	73.3	70.1
F17	56.1	63.0	67.2	67.9	70.8	67.8
F18	53.2	63.0	66.7	66.9	70.0	66.7
F19	53.7	60.7	63.9	67.6	67.2	64.8
F20	52.6	61.1	65.1	68.6	68.0	64.0

TABLE: 7A- ***IN VITRO*** **RELEASE DATA OF VALSARTAN FLOATING MATRIX TABLETS (F1 – F5)**

TIME IN HOURS	***CUMULATIVE % DRUG RELEASE ± SD* (n=3*)***				
	F1 (HPMC K100M 80%)	***F2 (HPMC K100M 75% + EC 5%)***	***F3 (HPMC K100M 70% + EC 10%)***	***F4 (HPMC K100M 65% + EC 15%)***	***F5 (HPMC K100M 60% + EC 20%)***
0.25	21.2 ± 0.29	22.0 ± 0.57	19.7 ± 0.47	21.5 ± 0.36	17.8 ± 0.29
0.50	22.5 ± 0.57	24.1 ± 0.49	22.0 ± 1.86	23.5 ± 0.57	19.4 ± 0.18
0.75	24.5 ± 0.75	26.7 ± 0.20	26.1 ± 0.49	25.6 ± 0.47	21.0 ± 0.93
1.0	26.9 ± 0.45	29.3 ± 0.16	27.9 ± 0.57	27.1 ± 0.38	23.3 ± 0.30
1.5	29.7 ± 0.53	33.2 ± 0.20	29.8 ± 0.40	28.7 ± 0.16	25.1 ± 0.67
2.0	32.6 ± 0.32	34.7 ± 0.36	31.5 ± 0.36	29.9 ± 0.20	27.5 ± 0.38
2.5	34.9 ± 0.29	36.1 ± 0.24	33.4 ± 0.28	31.2 ± 0.28	29.2 ± 0.24
3.0	36.8 ± 0.08	37.8 ± 0.14	35.4 ± 0.56	34.1 ± 0.36	30.2 ± 0.45
3.5	38.4 ± 0.30	38.6 ± 0.09	36.9 ± 0.56	35.2 ± 0.16	31.6 ± 0.44
4.0	41.8 ± 0.20	41.4 ± 0.29	38.8 ± 0.78	38.1 ± 1.14	33.2 ± 0.57
4.5	43.5 ± 0.43	42.7 ± 0.30	40.7 ± 0.87	39.5 ± 1.03	34.9 ± 0.16
5.0	44.7 ± 0.21	44.0 ± 0.09	42.9 ± 0.41	39.7 ± 2.06	36.6 ± 0.18
5.5	45.8 ± 0.14	45.1 ± 0.21	44.6 ± 0.46	42.1 ± 0.77	38.4 ± 0.21
6.0	48.0 ± 0.29	46.7 ± 0.29	46.6 ± 0.30	43.6 ± 0.74	40.1 ± 0.23
6.5	49.6 ± 0.28	48.6 ± 0.20	48.3 ± 0.12	44.9 ± 0.61	42.2 ± 0.36
7.0	52.2 ± 0.14	52.5 ± 0.16	50.4 ± 0.37	46.2 ± 0.12	44.0 ± 0.47
7.5	54.3 ± 0.24	54.4 ± 0.57	52.4 ± 0.28	47.7 ± 0.16	45.9 ± 0.29
8.0	57.7 ± 0.43	57.9 ± 1.88	54.8 ± 0.58	49.4 ± 0.14	47.7 ± 0.23
8.5	59.8 ± 0.44	61.3 ± 0.37	56.6 ± 0.65	50.9 ± 0.20	49.3 ± 0.12
9.0	61.4 ± 0.26	62.1 ± 0.20	58.7 ± 0.55	55.7 ± 1.22	50.9 ± 0.23
9.5	63.6 ± 0.20	64.3 ± 0.40	60.4 ± 0.77	56.9 ± 0.41	54.1 ± 0.78
10.0	65.7 ± 0.24	65.4 ± 0.30	63.2 ± 0.72	59.2 ± 0.53	56.5 ± 0.36
10.5	67.8 ± 0.44	67.3 ± 0.36	65.6 ± 1.39	62.9 ± 1.42	59.3 ± 0.29
11.0	70.4 ± 0.08	70.6 ± 0.16	68.8 ± 1.94	63.6 ± 0.82	61.5 ± 0.24
11.5	71.9 ± 0.44	72.6 ± 0.14	70.8 ± 1.79	68.0 ± 0.30	63.6 ± 0.29
12.0	75.3 ± 0.16	74.5 ± 0.36	73.3 ± 0.70	71.3 ± 0.53	67.1 ± 0.80

TABLE: 7B- *IN VITRO* RELEASE DATA OF VALSARTAN FLOATING MATRIX TABLETS (F6 – F10)

TIME IN HOURS	***CUMULATIVE % DRUG RELEASE ± SD* (n=3*)***				
	F6 (HPMC K4M 80%)	***F7 (HPMC K4M 75% + EC 5%)***	***F8 (HPMC K4M 70% + EC 10%)***	***F9 (HPMC K4M 65% + EC 15%)***	***F10 (HPMC K4M 60% + EC 20%)***
0.25	22.8 ± 0.57	21.5 ± 0.45	16.1 ± 0.47	18.4 ± 0.16	21.5 ± 0.20
0.50	24.4 ± 0.94	23.3 ± 0.56	18.2 ± 1.12	19.9 ± 0.47	24.0 ± 0.67
0.75	26.4 ± 1.18	25.9 ± 0.73	20.3 ± 1.90	21.7 ± 0.47	25.5 ± 0.61
1.0	28.6 ± 1.10	28.1 ± 0.45	23.3 ± 1.99	25.3 ± 1.85	27.4 ± 0.52
1.5	30.7 ± 0.69	30.5 ± 0.35	25.5 ± 2.22	26.5 ± 1.76	30.0 ± 0.87
2.0	33.2 ± 0.49	32.5 ± 0.12	27.8 ± 2.20	28.6 ± 1.80	31.6 ± 1.25
2.5	35.1 ± 0.47	34.2 ± 0.12	30.1 ± 2.45	31.5 ± 2.97	33.3 ± 1.12
3.0	37.1 ± 1.08	36.2 ± 0.47	32.0 ± 3.22	33.4 ± 2.73	34.8 ± 0.80
3.5	39.5 ± 1.13	38.9 ± 0.20	33.8 ± 3.30	35.7 ± 3.23	37.0 ± 1.18
4.0	42.0 ± 1.63	42.0 ± 0.57	36.7 ± 3.42	38.6 ± 3.26	40.2 ± 1.13
4.5	44.7 ± 2.36	44.0 ± 0.93	38.6 ± 3.47	40.8 ± 3.30	42.5 ± 1.06
5.0	47.4 ± 2.36	46.1 ± 1.02	40.6 ± 3.80	43.7 ± 4.00	45.2 ± 1.57
5.5	50.6 ± 2.61	48.8 ± 1.75	43.2 ± 3.31	44.9 ± 3.94	48.0 ± 1.72
6.0	53.3 ± 2.49	51.5 ± 1.81	46.4 ± 3.24	47.8 ± 3.63	50.6 ± 2.20
6.5	55.7 ± 2.73	55.0 ± 0.84	49.3 ± 3.46	51.4 ± 4.51	53.1 ± 2.12
7.0	58.0 ± 2.88	57.4 ± 1.43	52.3 ± 3.16	53.9 ± 3.63	55.9 ± 2.66
7.5	60.3 ± 2.70	60.8 ± 1.40	55.7 ± 3.44	57.4 ± 4.51	59.1 ± 2.68
8.0	62.9 ± 2.74	63.8 ± 1.15	58.5 ± 3.36	60.2 ± 3.63	61.8 ± 2.05
8.5	65.9 ± 1.75	66.6 ± 1.21	60.9 ± 3.31	62.2 ± 4.46	64.1 ± 1.98
9.0	68.3 ± 1.79	69.3 ± 0.86	63.9 ± 3.72	65.5 ± 3.70	67.7 ± 1.73
9.5	71.0 ± 2.01	71.7 ± 0.62	66.8 ± 3.47	68.3 ± 3.66	70.1 ± 1.03
10.0	73.4 ± 1.94	74.7 ± 0.08	69.4 ± 2.79	70.2 ± 3.81	72.0 ± 0.96
10.5	76.8 ± 2.38	77.8 ± 0.30	72.1 ± 2.90	73.1 ± 3.14	74.0 ± 1.10
11.0	80.1 ± 2.28	79.9 ± 0.57	75.4 ± 2.35	76.2 ± 3.28	76.9 ±1.12
11.5	82.5 ± 1.76	82.0 ± 0.21	78.2 ± 1.64	80.0 ± 2.78	79.4 ± 0.35
12.0	85.6 ± 0.68	84.0 ± 0.30	83.6 ± 1.51	82.5 ± 3.22	81.3 ± 0.36

TABLE: 7C- *IN VITRO* RELEASE DATA OF VALSARTAN FLOATING MATRIX TABLETS (F11 – F15)

TIME IN HOURS	***CUMULATIVE % DRUG RELEASE ± SD* (n=3*)***				
	F11 (HPMC K15M 80%)	***F12 (HPMC K15M 75% + EC 5%)***	***F13 (HPMC K15M 70% + EC 10%)***	***F14 (HPMC K15M 65% + EC 15%)***	***F15 (HPMC K15M 60% + EC 20%)***
0.25	24.1 ± 0.29	17.8 ± 0.38	19.1 ± 0.24	17.8 ± 0.29	21.5 ± 0.47
0.50	25.8 ± 0.16	19.4 ± 0.18	21.5 ± 0.53	19.2 ± 0.57	23.2 ± 0.14
0.75	27.2 ± 0.65	23.6 ± 0.89	24.5 ± 0.08	21.4 ± 1.22	25.4 ± 0.36
1.0	29.3 ± 0.29	25.7 ± 0.56	27.0 ± 0.57	24.3 ± 0.74	27.6 ± 0.49
1.5	30.9 ± 0.23	26.9 ± 0.57	30.0 ± 0.28	26.2 ± 0.29	29.9 ± 0.42
2.0	32.5 ± 0.09	29.2 ± 0.49	33.4 ± 0.54	28.0 ± 0.73	32.5 ± 0.24
2.5	34.2 ± 0.09	30.7 ± 0.36	35.5 ± 0.20	29.8 ± 0.98	35.8 ± 0.37
3.0	35.8 ± 0.23	33.2 ± 1.53	37.8 ± 0.44	31.7 ± 1.07	37.7 ± 0.28
3.5	38.1 ± 0.66	35.5 ± 1.51	39.1 ± 0.40	34.3 ± 1.09	39.4 ± 0.09
4.0	40.3 ± 1.02	37.8 ± 1.45	42.0 ± 0.12	37.2 ± 0.98	41.6 ± 0.16
4.5	42.3 ± 0.49	40.0 ± 0.54	43.8 ± 0.53	39.8 ± 1.43	43.8 ± 0.52
5.0	44.3 ± 0.57	42.6 ± 0.57	45.5 ± 0.20	42.9 ± 0.84	45.5 ± 0.49
5.5	47.5 ± 0.74	44.9 ± 0.53	47.6 ± 0.28	45.0 ± 0.66	47.1 ± 0.29
6.0	51.0 ± 1.93	47.4 ± 0.37	50.1 ± 0.24	47.4 ± 0.24	48.4 ± 0.23
6.5	54.1 ± 0.99	51.3 ± 0.47	52.1 ± 0.29	48.6 ± 0.45	51.0 ± 0.43
7.0	56.5 ± 0.97	53.8 ± 0.45	53.4 ± 0.69	51.6 ± 0.30	52.8 ± 0.13
7.5	58.9 ± 1.02	55.7 ± 0.38	56.7 ± 1.13	53.7 ± 0.16	54.8 ± 0.36
8.0	61.2 ± 0.97	57.5 ± 0.59	59.2 ± 0.97	56.6 ± 0.60	56.1 ± 0.12
8.5	63.5 ± 0.75	59.4 ± 0.73	61.0 ± 1.06	59.5 ± 0.20	58.4 ± 0.32
9.0	65.9 ± 0.88	62.7 ± 1.92	63.1 ± 0.99	62.6 ± 0.57	60.7 ± 0.71
9.5	68.4 ± 1.08	65.5 ± 1.03	65.7 ± 1.39	65.1 ± 0.57	62.5 ± 0.57
10.0	71.1 ± 0.80	68.3 ± 1.63	68.2 ± 1.63	67.5 ± 0.86	64.9 ± 0.33
10.5	73.2 ± 0.77	70.8 ± 1.82	71.0 ± 1.84	69.8 ± 0.14	67.5 ± 0.16
11.0	76.0 ± 0.14	73.4 ± 2.14	73.1 ± 0.58	72.0 ± 0.89	70.4 ± 0.57
11.5	78.2 ± 0.32	75.6 ± 1.48	75.6 ± 0.60	74.7 ± 0.59	73.5 ± 0.85
12.0	80.6 ± 0.59	79.6 ± 0.75	78.6 ± 0.59	77.7 ± 0.68	76.6 ± 0.98

TABLE: 7D- *IN VITRO* RELEASE DATA OF VALSARTAN FLOATING MATRIX TABLETS (F16 – F20)

TIME IN HOURS	***CUMULATIVE % DRUG RELEASE ± SD* (n=3*)***				
	F16 (MC 75%)	***F17 (MC 70% + EC 5%)***	***F18 (MC 65% + EC 10%)***	***F19 (MC 60% + EC 15%)***	***F20 (MC 55% + EC 20%)***
0.25	19.6 ± 0.38	17.0 ± 0.80	15.6 ± 0.24	16.5 ± 0.38	17.3 ± 0.84
0.50	22.5 ± 0.38	20.2 ± 0.54	18.2 ± 1.15	19.7 ± 0.52	19.2 ± 0.45
0.75	25.0 ± 0.45	25.4 ± 0.31	22.1 ± 1.83	25.2 ± 0.42	21.8 ± 1.02
1.0	27.0 ± 0.46	27.8 ± 0.36	25.6 ± 0.96	26.9 ± 0.36	24.3 ± 0.77
1.5	30.4 ± 0.63	29.8 ± 0.28	28.2 ± 1.52	30.8 ± 0.20	26.6 ± 1.31
2.0	33.6 ± 0.24	33.2 ± 0.47	30.7 ± 1.62	32.8 ± 0.26	28.8 ± 1.91
2.5	35.2 ± 1.00	36.4 ± 0.29	34.5 ± 1.18	36.1 ± 0.38	31.2 ± 2.15
3.0	39.1 ± 1.17	40.2 ± 0.41	36.4 ± 1.43	38.8 ± 0.57	33.0 ± 2.32
3.5	41.2 ± 0.54	41.6 ± 0.16	39.5 ± 1.60	41.2 ± 0.28	35.8 ± 2.28
4.0	44.2 ± 0.74	44.9 ± 0.16	42.0 ± 1.78	44.5 ± 0.29	38.3 ± 2.82
4.5	45.2 ± 0.67	49.1 ± 2.40	45.2 ± 1.96	47.4 ± 0.57	40.8 ± 2.15
5.0	46.8 ± 0.12	53.6 ± 1.66	48.1 ± 3.08	51.9 ± 0.74	43.4 ± 1.67
5.5	48.5 ± 0.24	56.4 ± 1.60	51.6 ± 3.23	55.6 ± 0.40	45.5 ± 1.81
6.0	51.2 ± 0.23	59.5 ± 1.46	55.8 ± 2.00	58.8 ± 0.42	47.3 ± 2.37
6.5	53.6 ± 0.63	62.3 ± 1.65	58.4 ± 2.24	61.5 ± 0.67	50.9 ± 2.53
7.0	57.0 ± 0.29	65.4 ± 1.17	61.1 ± 3.08	64.3 ± 0.20	54.0 ± 2.61
7.5	60.1 ± 0.49	67.8 ± 1.12	64.2 ± 2.41	67.0 ± 0.37	57.1 ± 2.81
8.0	62.7 ± 0.16	71.0 ± 1.58	67.1 ± 1.73	69.3 ± 0.49	59.9 ± 2.34
8.5	65.9 ± 0.17	73.5 ± 1.38	69.8 ± 2.28	72.5 ± 1.05	62.7 ± 2.81
9.0	68.8 ± 0.52	76.4 ± 0.75	72.2 ± 2.06	74.5 ± 0.49	65.9 ± 2.44
9.5	72.1 ± 0.50	78.3 ± 1.58	74.4 ± 1.98	76.8 ± 0.26	68.9 ± 2.53
10.0	75.1 ± 0.57	80.5 ± 1.38	76.7 ± 1.22	78.6 ± 0.22	72.1 ± 2.49
10.5	77.9 ± 0.49	82.3 ± 0.75	78.9 ± 0.86	80.7 ± 0.46	74.6 ± 2.92
11.0	83.0 ± 0.37	84.6 ± 1.58	81.8 ± 0.53	82.9 ± 0.17	78.6 ± 2.33
11.5	86.8 ± 0.84	86.6 ± 1.11	84.2 ± 0.54	84.9 ± 0.37	80.8 ± 2.04
12.0	90.3 ± 0.65	89.7 ±0.30	88.0 ± 0.71	87.8 ± 0.36	86.7 ± 1.24

TABLE: 8A- *IN VITRO* RELEASE KINETICS DATA OF VALSARTAN FLOATING MATRIX TABLETS (F1 – F10)

FORMULATION CODE	***ZERO ORDER***		***FIRST ORDER***		***HIGUCHI***		***KORSMEYER PEPPAS***		***HIXSON CROWELL***		***RELEASE MECHANISM***
	r^2	$K^0 (h^{-1})$	r^2	$K_1 (h^{-1})$	r^2	$K_H (h^{-1/2})$	r^2	n	r^2	$K_{HC} (h^{-1/3})$	
F1	0.977	2.382	0.954	-0.038	0.979	18.01	0.973	0.459	0.936	-0.107	NFD
F2	0.969	2.325	0.941	-0.037	0.981	17.25	0.959	0.524	0.949	-0.104	NFD
F3	0.969	4.490	0.943	-0.036	0.983	17.18	0.964	0.451	0.944	-0.101	NFD
F4	0.945	4.113	0.930	-0.031	0.963	15.48	0.936	0.497	0.906	-0.089	NFD
F5	0.993	3.855	0.965	-0.029	0.992	15.77	0.949	0.452	0.927	-0.087	NFD
F6	0.963	5.524	0.942	-0.054	0.972	21.31	0.956	0.470	0.921	-0.142	NFD
F7	0.967	5.613	0.953	-0.054	0.977	21.73	0.959	0.483	0.924	-0.144	NFD
F8	0.979	5.618	0.935	-0.050	0.966	22.01	0.948	0.453	0.938	-0.137	NFD
F9	0.976	5.566	0.948	-0.050	0.974	21.73	0.954	0.518	0.932	-0.137	NFD
F10	0.965	5.381	0.961	-0.049	0.980	20.77	0.953	0.573	0.914	-0.133	NFD

NFD- NON-FICKIAN DIFFUSION

TABLE: 8B- *IN VITRO* RELEASE KINETICS DATA OF VALSARTAN FLOATING MATRIX TABLETS (F11 – F20)

FORMULATION CODE	***ZERO ORDER***		***FIRST ORDER***		***HIGUCHI***		***KORSMEYER PEPPAS***		***HIXSON CROWELL***		***RELEASE MECHANISM***
	r^2	$K^0 (h^{-1})$	r^2	$K_1 (h^{-1})$	r^2	$K_H (h^{-1/2})$	r^2	n	r^2	$K_{HC} (h^{-1/3})$	
F11	0.959	5.138	0.955	-0.047	0.978	19.61	0.947	0.541	0.894	-0.126	NFD
F12	0.970	5.249	0.960	-0.045	0.980	20.44	0.959	0.464	0.939	-0.118	NFD
F13	0.970	4.995	0.953	-0.043	0.986	19.38	0.976	0.475	0.976	-0.122	NFD
F14	0.973	5.219	0.967	-0.044	0.984	20.37	0.960	0.471	0.937	-0.122	NFD
F15	0.966	4.632	0.941	-0.038	0.982	17.76	0.966	0.484	0.971	-0.107	NFD
F16	0.966	5.820	0.887	-0.061	0.949	22.60	0.942	0.462	0.941	-0.156	NFD
F17	0.970	6.306	0.967	-0.069	0.989	25.04	0.981	0.520	0.982	-0.173	NFD
F18	0.976	6.178	0.961	-0.062	0.983	24.54	0.976	0.537	0.980	-0.079	NFD
F19	0.976	6.164	0.966	-0.064	0.986	24.47	0.980	0.515	0.975	-0.165	NFD
F20	0.978	5.772	0.919	-0.054	0.958	22.57	0.952	0.539	0.947	-0.146	NFD

NFD- NON-FICKIAN DIFFUSION

TABLE: 9 STABILITY STUDY (40^0C/75% RH) OF BEST FORMULATION (F5)

PARAMETERS	INTERVALS OF TESTING (OBSERVATION)			
	AT 0 MONTH	AT 1st MONTH	AT 2nd MONTH	AT 3rd MONTH
Physical Appearance	White colour, biconvex shaped	White colour, biconvex shaped	White colour, biconvex shaped	White colour, biconvex shaped
Hardness (kg/cm^2)	4	4	4	4
Diameter (mm)	10	10	10	10
Thickness (mm)	4	4	4	4
Friability (%)	0.28	0.27	0.25	0.24
Weight variation (mg)	249.03	249.00	248.37	248.07
Drug content (%)	99.79	99.20	98.70	98.00
Floating lag time	Floats immediately	Floats immediately	Floats immediately	Floats immediately
Total floating time (hours)	>24hrs	>24hrs	>24hrs	>24hrs

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